



An overview on medicinal perspective of thiazolidine-2,4-dione: A remarkable scaffold in the treatment of type 2 diabetes

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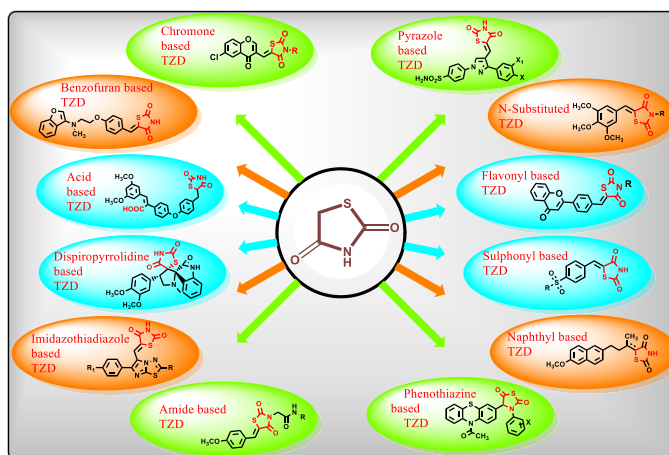
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HIGHLIGHTS

- TZDs, an important pharmacophore in the treatment of diabetes.
- Various analog-based synthetic strategies and biological significance are discussed.
- Clinical studies using TZDs along with other antidiabetic agents are also highlighted.
- SAR has been discussed to suggest the interactions between derivatives and receptor sites.
- Pyrazole, chromone, and acid-based TZDs can be considered as potential lead molecules.

GRAPHICAL ABSTRACT



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ABSTRACT

Diabetes or diabetes mellitus is a complex or polygenic disorder, which is characterized by increased levels of glucose (hyperglycemia) and deficiency in insulin secretion or resistance to insulin over an elongated period in the liver and peripheral tissues. Thiazolidine-2,4-dione (TZD) is a privileged scaffold and an outstanding heterocyclic moiety in the field of drug discovery, which provides various opportunities in

Abbreviations: ADDP, 1,1'-(Azodicarbonyl)dipiperidine; AF, activation factor; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; Boc, Butyloxycarbonyl; DNA, deoxyribonucleic acid; DBD, DNA-binding domain; DM, diabetes mellitus; DCM, dichloromethane; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; *E*, Entgegen; ECG, electrocardiogram; FDA, food and drug administration; FFA, free fatty acid; GAL4, Galactose transporter type; GLUT4, glucose transporter type 4; GPT, glutamic pyruvic transaminase; HCl, Hydrochloric Acid; HDL, high-density lipoprotein; HEp-2, Human epithelial type 2; HFD, high-fat diet; HEK, human embryonic kidney; i.m, Intramuscular; INS-1, insulin-secreting cells; IL- β , interleukin-beta; IDF, international diabetes federation; K₂CO₃, Potassium carbonate; LBD, ligand-binding domain; LDL, low-density lipoprotein; MDA, malondialdehyde; mCPBA, meta-chloroperoxybenzoic acid; NBS, N-bromosuccinimide; NaH, Sodium Hydride; NA, nicotinamide; NO, nitric oxide; NF κ B, nuclear factor kappa-B; OGTT, oral glucose tolerance test; PPAR, peroxisome-proliferator activated receptor; PPRE, peroxisome proliferator response element; Pd, Palladium; PDB, protein data bank; PTP1B, protein-tyrosine phosphatase 1B; KOH, potassium hydroxide; QSAR, quantitative structure-activity relationship; RXR, retinoid X receptor; STZ, streptozotocin; SAR, structure-activity relationship; T2DM, type 2 diabetes mellitus; THF, tetrahydrofuran; TZD, thiazolidine-2,4-dione; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TG, triglycerides; TNF- α , tumor necrosis factor-alpha; WAT, white adipose tissue; Z, Zusammen.

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exploring this moiety as an antidiabetic agent. In the past few years, various novel synthetic approaches had been undertaken to synthesize different derivatives to explore them as more potent antidiabetic agents with devoid of side effects (i.e., edema, weight gain, and bladder cancer) of clinically used TZD (pioglitazone and rosiglitazone). In this review, an effort has been made to summarize the up to date research work of various synthetic strategies for TZD derivatives as well as their biological significance and clinical studies of TZDs in combination with other category as antidiabetic agents. This review also highlights the structure-activity relationships and the molecular docking studies to convey the interaction of various synthesized novel derivatives with its receptor site.

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Introduction

In this modernized industrial world, the ever-growing population rate along with physical inactivity of people has put the life of mankind on an edge of being targeted by various diseases among which diabetes is the most common one. According to the International Diabetes Federation (IDF), the morbidity rate of this insidious disease has been estimated to show an increase from 425 million in 2017 to 629 million by 2045 [1]. Diabetes or diabetes mellitus (DM) is a complex or polygenic disorder which is characterized by increased levels of glucose (hyperglycemia) resulting from defects in insulin secretion, action or both (resistance) to insulin over an elongated period in the liver and peripheral tissues. DM is classified as type 1 i.e. insulin-dependent, type 2 i.e. non-insulin dependent and gestational diabetes (in pregnant women) [2,3]. The symptoms include polyuria, tiredness, dehydration, polyphagia, and polydipsia [4]. Therefore, it is necessary to maintain the proper blood glucose level, mainly during the early stages of diabetes. Several types of anti-hyperglycaemic agents are used as monotherapy or combination therapy to treat DM. These include meglitinides, biguanides, sulphonylurea, and α -glucosidase inhibitors. In addition to these, sesquiterpenoids have also been reported as potential anti-diabetic agents by virtue of protecting β -pancreatic cells and improving insulin secretion [5]. The treatment of type 2 diabetes mellitus (T2DM) has been reformed with the origin of thiazolidine-2,4-diones (TZDs) class of molecules that bring down the increased levels of blood glucose to normal [6].

TZDs also called as glitazones are the heterocyclic ring system consisting of five-membered thiazolidine moiety having carbonyl groups at 2 and 4 positions. Various substitutions can only be done at third and fifth positions. A comprehensive research has been done on TZDs resulting in various derivatives [7]. Though, substantial evidence reported with TZDs but none of them have reported up to date review and clinical studies of TZD [7–9]. In this review, we aimed to present the information from synthetic, *in vitro*, and *in vivo* studies that had been carried out on various TZD derivatives by collecting research journals published from the date of discovery of TZD in the early 1980s. In addition, we have discussed their molecular target (peroxisome proliferator-activated receptors, PPAR- γ), toxicity profiling (hepatotoxicity and cardiotoxicity) and their structure–activity relationship (SAR). Further, we have compiled clinical studies of TZDs that had been done in combination with other categories as antidiabetic agents. We believe that this review will provide sound knowledge, and guidance to carry out further research on this scaffold to mitigate the problems of clinically used TZDs.

The general procedure for synthesizing TZDs has been shown in **S1**. TZDs (3) has been synthesized by refluxing thiourea (1) with

chloroacetic acid (2) for 8–12 h at 100–110 °C, using water and conc. HCl as a solvent [10].

Antiquity of TZDs

The antihyperglycemic activity of TZDs came into notice by the entry of first drug, **ciglitazone** in the early 1980s but later on, it was withdrawn due to its liver toxicity. Then, **troglitazone** was discovered and developed by Sankyo Company in the year 1988. However, it caused hepatotoxicity, as a result, it was banned in 2000. In 1999, Takeda and Pfizer developed two drugs, **pioglitazone**, and **englitazone**. However, englitazone was discontinued due to its adverse effects on the liver. Conversely, pioglitazone was described to be safe on the hepatic system. Meanwhile, **rosiglitazone** and **darglitazone** developed by Smithkline and Pfizer. However, darglitazone was terminated in the year 1999. Reports in 2001 revealed that rosiglitazone had shown to cause heart failure due to fluid retention and was first restricted by Food and Drug Administration (FDA) in 2010, later on in 2013 in a trial, it fails to show any effect on heart attack, and therefore restriction was removed by FDA (Fig. 1). The structure of various clinically reported TZDs is shown in Fig. 2 [11–13] and the studies, which were carried out in diabetic patients are presented in Table 1 [14–61].

Structure and biological functions of PPAR- γ in diabetes

Peroxisome proliferator-activated receptors (PPARs) are the transducer proteins belonging to the superfamily of steroid/thyroid/retinoid receptors, which is involved in many processes when activated by a specific ligand. These receptors were recognized in the 1990s in rodents. PPARs help in regulating the expression of various genes that are essential for lipid and glucose metabolism [62,63].

The structure of PPAR consists of four domains, namely A/B, C, D and E/F (Fig. 3A). The NH₂-terminal A/B domain consists of ligand-independent activation function 1 (AF-1) liable for the phosphorylation of PPAR. The C domain is the DNA binding domain (DBD) having 2-zinc atoms responsible for the binding of PPAR to the peroxisome proliferator response element (PPRE) in the promoter region of target genes. The D site is responsible for the modular union of the DNA receptor and its corepressors. The E/F domain is the ligand-binding domain (LBD) consists of the AF-2 region used to heterodimerize with retinoid X receptor (RXR), thereby regulating the gene expression [64,65]. There are three major isoforms of PPAR: PPAR- α , PPAR- δ/β , and PPAR- γ . Their distribution in tissues, biological functions, and their agonists are shown in Table 2 [62–65].

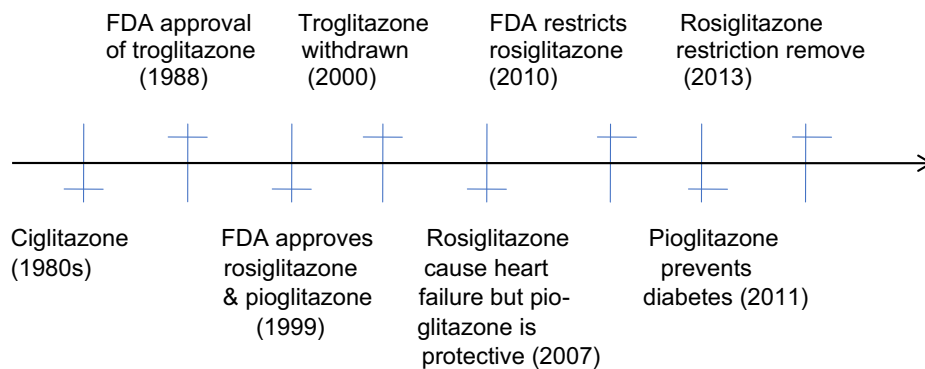


Fig. 1. The history of TZDs (modified and), adapted from [13].

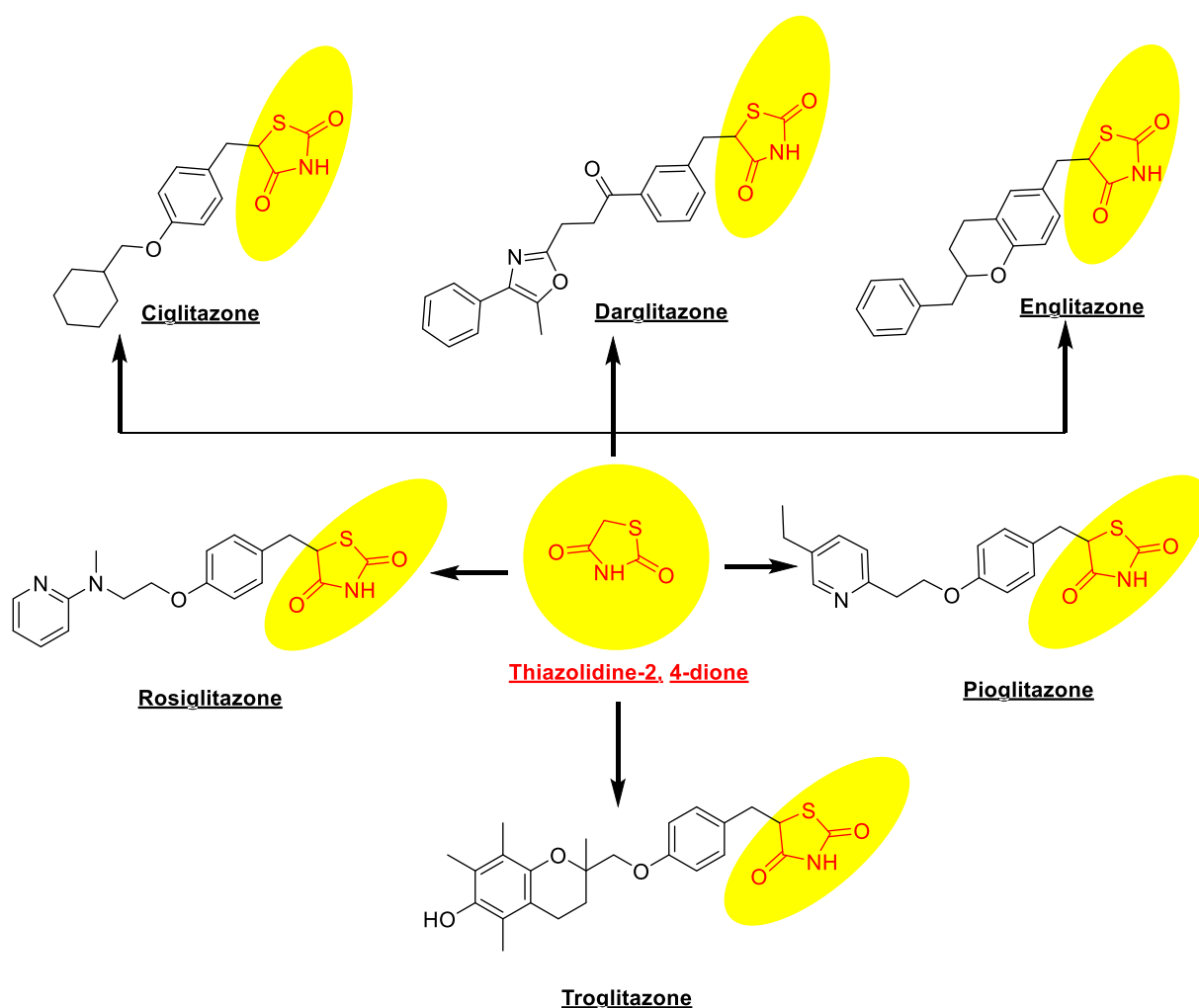


Fig. 2. Chemical structures of clinically used thiazolidine-2, 4-dione compounds (structures are original and made by using chem draw ultra 12.0).

Effects of TZDs on PPAR- γ molecular pathways involved in diabetes

The efficacy of PPAR- γ agonists in the management of insulin resistance and T2DM has been confirmed by a number of important experimental assays with TZDs [62]. TZDs act as the selective agonists of PPAR- γ . PPARs regulate the gene transcription by two mechanisms: **transactivation** (DNA dependent) and **transrepression** (DNA independent) [65]. In transactivation, when TZDs bind

to PPAR- γ , it gets activated and binds to 9-cis RXR, thereby forming a heterodimer [66]. This causes the binding of PPAR- γ -RXR complex to PPRE in target genes, which further regulates the genetic transcription and translation of various proteins that are indulged in cellular differentiation and glucose and lipid metabolism [67]. In transrepression, PPARs negatively interact with other signal-transduction pathways, such as nuclear factor kappa beta (NF κ B) pathway that controls many genes involved in inflammation,

Table 1
Efficacy of TZDs in diabetes in clinical trials.

Clinical Trial No.	Population Size	Status	Interventions	Phase	End Point	Reference
NCT00396227	2665	Completed	1. Vildagliptin add- on to metformin 2. TZD (pioglitazone, rosiglitazone) add on to metformin	Phase 3	<ul style="list-style-type: none"> • Mean change in HbA(1c) was $-0.68 \pm 0.02\%$ in the vildagliptin group and $-0.57 \pm 0.03\%$ in the TZD group. • Body weight increased in the TZD group (0.33 ± 0.11 kg) and decreased in the vildagliptin group (-0.58 ± 0.09 kg). • Adverse events were similar in both groups (vildagliptin: 39.5% and TZD: 36.3%). 	[14]
NCT02653209	600	Undergoing	1. Sitagliptin, 2. Canagliflozin 3. Pioglitazone	Phase 4	<ul style="list-style-type: none"> • HbA(1c) in obese patients (BMI > 30 kg/m²) was compared to non-obese patients. • Test the hypothesis that the patients with BMI > 30 kg/m² respond well to pioglitazone, and less well to sitagliptin in comparison to non-obese patients or not. • On treatment HbA(1c) levels in patients with an eGFR < 90 mL/min/1.73 m² compared to patients with an eGFR > 90 mL/min/1.73 m². • Test the hypothesis that the patients with modestly reduced eGFR (60–90 mL/min/1.73 m²) respond poorly to canagliflozin, and well to sitagliptin in comparison to eGFR > 90 mL/min/1.73 m² eGFR or not. • Prevalence of side effects: weight gain, hypoglycemia, edema, genital tract infection and discontinuation of therapy. • HbA(1c) therapy vs. predefined test of gender heterogeneity (i.e., Females are likely to show an improved response relative to males for pioglitazone). 	[15]
NCT00743002	87	Completed	1. TT223 with Metformin and/or TZD 2. Placebo with Metformin and/or TZD	Phase 2	<ul style="list-style-type: none"> • The safety and tolerability of TT223 was evaluated at 1 mg, 2 mg and 3 mg. • The efficacy of TT223 was evaluated in terms of changes in HbA(1c) value, fasting glucose levels vs. placebo group. • Determining the pharmacokinetic parameter of TT223 in patients. 	[26]
NCT01026194	204	Completed	1. Placebo/Teneligliptin + pioglitazone 2. Teneligliptin/Teneligliptin + pioglitazone	Phase 3	<ul style="list-style-type: none"> • The changes in HbA(1c) were greater ($-0.9 \pm 0.0\%$) in the teneligliptin group than that in the placebo group ($-0.2 \pm 0.0\%$). • The change in FPG was greater in the teneligliptin group than that in the placebo group. 	[37]
NCT00879970	1332	Terminated	1. Pioglitazone 2. Rosiglitazone 3. Placebo 4. Vitamin D placebo 5. Vitamin D	Phase 4	<ul style="list-style-type: none"> • Cardiovascular outcome (MI, stroke or cardiovascular death) is more in the placebo than in the treatment groups [TZD arm (0.4%) than Vitamin D arm (0.3%)]. • Hospitalization due to cancer is more in the placebo vs. Vitamin D arm. 	[48]

Table 1 (continued)

Clinical Trial No.	Population Size	Status	Interventions	Phase	End Point	Reference
NCT00676338	820	Completed	1. Exenatide (once weekly) 2. Metformin 3. Sitagliptin 4. Pioglitazone 5. Placebo	Phase 3	<ul style="list-style-type: none"> • Exenatide was non-inferior to metformin but superior to sitagliptin, and pioglitazone with regard to HbA(1c) reduction. • Exenatide and metformin provided similar improvements in glycemic control along with the benefit of weight reduction and no increased risk of hypoglycemia. • Weight gain was observed in the pioglitazone group. 	[57]
NCT00683878	972	Completed	1. Dapagliflozin (5 mg) + TZD 2. Dapagliflozin (10 mg) + TZD 3. Placebo matching dapagliflozin + pioglitazone	Phase 3	<ul style="list-style-type: none"> • The mean reduction in HbA(1c) was higher for arm 1 and 2 groups (−0.82 and −0.97%) vs. placebo (−0.42%). • Pioglitazone alone had greater weight gain (3 kg) than those receiving plus pioglitazone in combination with dapagliflozin (0.7–1.4 kg). • Events of genital infection were reported with dapagliflozin (8.6–9.2%). 	[58]
NCT01135394	134	Completed	1. Pioglitazone	Phase 4	<ul style="list-style-type: none"> • Characterize the changes at the physiological, cellular and molecular levels after TZD treatment. • Define genes that are regulated by TZD response. • Identify the SNPs and haplotypes genes that are influenced by TZD. • Glycemic, lipoprotein profile, and weight were monitored. 	[59]
NCT00481429	12	Completed	1. Rosiglitazone 2. Diet control + metformin	NA	<ul style="list-style-type: none"> • The performance of baseline biochemical biomarkers (plasma and urine) in patients who respond to TZD therapy from those do not, through the changes in HbA(1c) at 12 weeks. • Changes in baseline levels of key biochemical markers. • Effect of treatment on various novel predictive biomarkers and markers of insulin sensitivity. 	[60]
NCT00295633	565	Completed	1. Saxagliptin 2.5 mg + Pioglitazone 30 mg + Rosiglitazone 4 mg + Metformin 500–2500 mg 2. Saxagliptin 5 mg + Pioglitazone 30 mg + Rosiglitazone 4 mg + Metformin 500–2500 mg 3. Placebo + Pioglitazone + Rosiglitazone + Metformin	Phase 3	<ul style="list-style-type: none"> • Mean changes from baseline HbA(1c) was more in saxagliptin (−0.66% and −0.94% for 2.5 and 5 mg, respectively) than that in placebo group (−0.30%). • Plasma glucose level was also significantly reduced in the saxagliptin group than that in the placebo group. • Hypoglycemic events were similar between groups. 	[61]
NCT00308373	73	Completed	1. Metformin 2. Pioglitazone	NA	<ul style="list-style-type: none"> • Impact of TZD on the levels of cortisol. • Effect of TZD on breathing or sleepiness in patients with type 2 diabetes. 	[16]
NCT01055223	98,483	Completed	1. TZD only (rosiglitazone or pioglitazone or troglitazone) 2. TZD + spironolactone 3. TZD + amiloride	NA	<ul style="list-style-type: none"> • Impact on the fracture number/number of fracture of hand/foot/upper arm/wrist fracture and hip in both males and females after 6 and 12-months treatment. 	[17]

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Table 1 (continued)

Clinical Trial No.	Population Size	Status	Interventions	Phase	End Point	Reference
NCT00637273	514	Completed	1. Exenatide (once weekly) 2. Sitagliptin 3. Pioglitazone 4. Placebo tablet 5. Placebo once weekly	Phase 3	<ul style="list-style-type: none"> • Greater reduction of HbA(1c) in exenatide (−1.5%) than sitagliptin (−0.9%) or pioglitazone (−1.2%). • Weight loss was greater with exenatide (−2.3 kg) than sitagliptin (−1.5 kg) or pioglitazone (−5.1 kg). • Major adverse events were nausea and diarrhea with exenatide and sitagliptin. 	[18]
NCT00953498	40	Completed	1. Pioglitazone 2. Rosiglitazone	Phase 4	<ul style="list-style-type: none"> • HDL from control subjects had significantly shown to reduce the inhibitory effect of oxidised LDL on vasodilatation ($E_{max} = 77.6 \pm 12.9$ vs. $59.5 \pm 7.7\%$), whereas HDL from type 2 diabetic patients had no effect ($E_{max} = 52.4 \pm 20.4$ vs $57.2 \pm 18.7\%$). 	[19]
NCT02315287	190	Recruiting	1. Metformin + Sitagliptin + Pioglitazone 2. Metformin + Sitagliptin + Lobeglitazone	Phase 4	<ul style="list-style-type: none"> • Change in the level of HbA(1c). • Changes in β-cell function and insulin resistance after 1-year treatment. • Changes in FBS after 5 and 12 months. 	[20]
NCT01147627	416	Completed	1. Exenatide injection 2. Mixed protamine zinc recombinant human Insulin Lispro 25R 3. Pioglitazone	NA	<ul style="list-style-type: none"> • Changes in baseline value of HbA(1c) after 48-weeks • Percentage of patients achieving HbA(1c) (<6.5–7) and effect on fasting and postprandial plasma glucose concentration, blood pressure, lipid profiles. 	[21]
NCT00700856	3371	Active, not recruiting	1. Metformin + pioglitazone 2. Metformin + sulphonylureas (glibenclamide or gliclazide glimepiride)	Phase 4	<ul style="list-style-type: none"> • Safety and tolerability in various groups. • Hypoglycemia occurred less in the pioglitazone group (10%) than in the sulphonylurea group (34%). • Moderate weight gain (<2 kg) occurred in both groups. • Rate of adverse events such as heart failure, bladder cancer, and fractures was similar in both groups. 	[22]
NCT00329225	630	Completed	1. Rosiglitazone	Phase 4	<ul style="list-style-type: none"> • The decrease in HbA(1c), C-reactive protein, fibrinogen and matrix metalloproteinase 9 levels upon addition of rosiglitazone to insulin. 	[23]
NCT03646292	60	Not yet recruiting	1. Pioglitazone 2. Empagliflozin 3. Pioglitazone + empagliflozin	Phase 4	<ul style="list-style-type: none"> • Adverse events were mild to moderate. • Changes in liver fat through MRI-PDFF and liver fibrosis through MRE. • Changes in lipid profile, liver enzyme, glucose metabolism and inflammation status (CRP) were monitored. 	[24]
NCT02426294	154	Recruiting	1. Pioglitazone 2. Glimepiride	Phase 4	<ul style="list-style-type: none"> • Evidence of efficacy of glycemic control by HbA(1c). • Changes in insulin resistance by HOMA and lipid profile from baseline value after 26-weeks treatment. 	[25]
NCT00333723	245	Completed	1. Rosiglitazone	Phase 4	<ul style="list-style-type: none"> • Efficacy of rosiglitazone combined with glyburide to glyburide monotherapy upon FPG, c-peptide, HOMA and in reducing HbA(1c) after 24-weeks of the treatment period. 	[27]

Table 1 (continued)

Clinical Trial No.	Population Size	Status	Interventions	Phase	End Point	Reference
NCT02954692	111	Completed	<ol style="list-style-type: none"> 1. Insulin glargine 2. Metformin 3. Sulfonylurea 4. Meglitinides 5. TZDs 6. α-glucosidase inhibitors 7. GLP1 receptor agonist 8. DPP-4 inhibitors 9. SGLT-2 inhibitors 	Phase 4	<ul style="list-style-type: none"> • Changes from baseline in the levels of HbA (1c), SMBG, FPG and DTSQ scores at 12 and 24-weeks. • Percentage of patients reaching targeted fasting SMBG (80–130 mg/dL) at 12 and 24-weeks. 	[28]
NCT02475499	886,172	Completed	<ol style="list-style-type: none"> 1. DPP-4 inhibitors 2. GLP-1 analogs 3. Sulfonylureas 4. Biguanides 5. TZDs 6. α-glucosidase inhibitors 7. Meglitinides 	NA	<ul style="list-style-type: none"> • Number of increased risk of pancreatic cancer was measured while using incretin-based drugs in comparison with sulfonylureas. 	[29]
NCT01030679	214	Completed	<ol style="list-style-type: none"> 1. CKD-501 (Lobeglitazone) (0.5, 1 and 2 mg) 2. Placebo 	Phase 2	<ul style="list-style-type: none"> • Changes from baseline in the levels of FPG, glycemic and lipid parameters at 8-weeks. • Profiling of adverse events at 8-weeks. 	[30]
NCT01593371	98	Completed	<ol style="list-style-type: none"> 1. Metformin 2. Pioglitazone 	NA	<ul style="list-style-type: none"> • No changes in BMI while using pioglitazone and metformin. • Improvements in glycemia and insulin resistance. • Increase in chemerin levels. • Indices of glycemic control and insulin resistance were significantly improved by both groups after 3-months. • Both treatments are equally effective in reducing chemerin concentrations, a novel member of the adipokine family. • Did not alter waist circumference, weight or BMI by both drugs. 	[31]
NCT01223196	29	Completed	<ol style="list-style-type: none"> 1. Pioglitazone 2. Placebo 	Phase 4	<ul style="list-style-type: none"> • Improvements in glycaemic control, β-cell function and inflammatory indices (MCP-1, IL-6, FRK, hsCRP, and PAI) • Did not alter waist circumference, weight or BMI by both drugs. • Adiponectin levels and TACE enzymatic activity is significantly decreased by pioglitazone than in the placebo group. 	[32]
NCT00367055	84	Completed	<ol style="list-style-type: none"> 1. Rosiglitazone + metformin 2. Metformin 3. Metformin + gliclazide 	Phase 4	<ul style="list-style-type: none"> • Changes from baseline in the insulin secretory capacity, insulin resistance index (HOMA-IR) and β-cell function index (HOMA-beta) • Changes from baseline in HbA(1c), FBG, CPP total and incremental AUC and • Changes from baseline in CPP concentration peak and incremental concentration peak at the month of 36. 	[33]

(continued on next page)

Table 1 (continued)

Clinical Trial No.	Population Size	Status	Interventions	Phase	End Point	Reference
NCT02476760	1,417,914	Completed	<ol style="list-style-type: none"> 1. DPP-4 inhibitors 2. GLP-1analogs 3. Insulin 4. Biguanides 5. Sulfonylureas 6. TZDs 7. α-glucosidase inhibitors 8. Meglitinides 	NA	<ul style="list-style-type: none"> • No signs of acute pancreatitis while using incretin-based as compared to other oral antidiabetic drugs. 	[34]
NCT01468181	394	Completed	<ol style="list-style-type: none"> 1. LY2189265 (Dulaglutide) 2. Sulfonylureas 3. Biguanides 4. α-glucosidase inhibitor 5. TZD 6. Glinides 	Phase 3	<ul style="list-style-type: none"> • Percentage of participants with TEAE and hypoglycemic episodes from baseline to 52-weeks. • Changes from baseline in HbA(1c), FBG, SMBG, body weight, and HOMA2. 	[35]
NCT02027103	102	Completed	<ol style="list-style-type: none"> 1. Metformin 2. Pioglitazone 	NA	<ul style="list-style-type: none"> • Both medications were equally effective in reducing FBG, HbA(1c), fetuin-A and osteoprotegerin levels in both diabetic women and men. 	[36]
NCT02887625	410	NA	<ol style="list-style-type: none"> 1. Pioglitazone + exenatide 2. Insulin glargine 3. Insulin Aspart 	NA	<ul style="list-style-type: none"> • A great decrease in HbA(1c) ($6.1 \pm 0.1\%$ or 43 ± 0.7 mmol/mol) by combination therapy as compared to insulin therapy ($7.1 \pm 0.1\%$ or 54 ± 0.8 mmol/mol). • More weight gain and a higher rate of hypoglycemia in insulin therapy than in the combination therapy. 	[38]
NCT00373178	100	Completed	<ol style="list-style-type: none"> 1. Rosiglitazone 2. Metformin 3. Antidiabetic medications 	Phase 4	<ul style="list-style-type: none"> • Similar improvement in glycemic profile and apelin levels, whereas lipid parameters, fat mass, and visfatin remained almost unaffected by both rosiglitazone and metformin. • Significant improvement in plasma ghrelin level and reduction in HOMA-IR, hs-CRP and systolic blood pressure from baseline values in the rosiglitazone group than in the metformin group. • Improvement in cardiovascular risk profile. 	[39]
NCT01777282	374	Completed	<ol style="list-style-type: none"> 1. Albiglutide + Sulfonylurea 2. Albiglutide + Biguanide 3. Albiglutide + Glinide 4. Albiglutide + TZD 5. Albiglutide + α-glucosidase inhibitor 	Phase 3	<ul style="list-style-type: none"> • Common adverse effects were nasopharyngitis (32.6%), constipation (7.2%), and diabetic retinopathy (5.3%). • Hypoglycemia occurred in 6.4% of patients in the first and third groups. • More reduction from baseline in HbA(1c) was observed when albiglutide added to TZD than in the other groups, whereas, reductions in FBG levels were observed in all groups. • The slight increase from baseline in body weight was observed with the addition of albiglutide to TZD. 	[40]
NCT00225225	45	Terminated	<ol style="list-style-type: none"> 1. Rosiglitazone 2. Rosiglitazone + dietary recommendation for weight maintenance 	NA	<ul style="list-style-type: none"> • Change in weight from 270 +/- 54 lbs to 244 +/- 61 lbs was observed with a low-calorie diet and behavioral modification in patients treated with TZDs and is associated with glycemic and blood pressure control. 	[41]

Table 1 (continued)

Clinical Trial No.	Population Size	Status	Interventions	Phase	End Point	Reference
NCT00482183	38	Completed	1. Pioglitazone 2. Sirolimus-eluting stent	Phase 3	<ul style="list-style-type: none"> • No significant differences in glycemic control levels, lipid levels, and restenosis. • The HOMA-IR was significantly lowered and the incidence of major adverse cardiac events tended to be lower in the pioglitazone than in the sirolimus group after 1-yr therapy. 	[42]
NCT02285205	38	Completed	Lobeglitazone	Phase 4	<ul style="list-style-type: none"> • Significant decrease in controlled attenuation parameter values (313.4 dB/m at baseline vs. 297.8 dB/m) at 24-weeks. • Improvements in HbA(1c) values (6.56%), as well as the lipid and liver profiles and reduction in intrahepatic fat content, was observed in the treated patients. 	[43]
NCT00123643	36	Completed	1. Rosiglitazone 2. Glyburide	Phase 4	<ul style="list-style-type: none"> • Changes from baseline on flow-mediated dilation as a measure of endothelial function after 6-months of treatment. 	[44]
NCT02365233	5	Terminated	1. DPP4inhibitor 2. Pioglitazone 3. Lantus insulin	Phase 4	<ul style="list-style-type: none"> • Change in hepatic lipid content from baseline to 6-month follow up. 	[45]
NCT00575471	250	Completed	1. Rivoglitazone HCl (0.5, 1 and 1.5 mg) 2. Placebo	Phase 2	<ul style="list-style-type: none"> • Change in HbA(1c) and FPG from baseline for rivoglitazone as compared to placebo at 12-weeks. 	[46]
NCT02456428	1,499,650	Completed	1. DPP4 inhibitor 2. GLP-1 analogs 3. Insulins 4. Biguanides 5. Sulfonylureas 6. TZDs 7. α -glucosidase inhibitors 8. Meglitinides	NA	<ul style="list-style-type: none"> • The rate of hospitalization for heart failure did not increase with the use of incretin-based drugs as compared with oral antidiabetic-drug combinations among patients with heart failure. 	[47]
NCT00819325	50	Completed	1. Pioglitazone + Oral hypoglycemic agents (sulfonylurea or metformin) 2. Oral hypoglycemic agents	Phase 4	<ul style="list-style-type: none"> • Change in 3D-neointimal plaque volume at 6-months compared to baseline. • Change in the 2D-neointimal area within the stent at 6-months compared to baseline. 	[49]
NCT00994682	176	Completed	1. Pioglitazone study drug 2. Placebo 3. Pioglitazone open label	Phase 4	<ul style="list-style-type: none"> • Pioglitazone treatment caused a significant improvement in individual fibrosis score (-0.5); reduced hepatic triglyceride content (7%) and improved adipose tissue, hepatic, and muscle insulin sensitivity. • The resolution of NASH was observed a greater number of patients treated with active drug treatment. • The rate of adverse events was similar between the groups, although weight gain was more in the pioglitazone group. 	[50]
NCT02730377	1994	Active, not recruiting	1. Liraglutide add on to metformin 2. Oral antidiabetics (α -glucosidase inhibitors+ DPP4 inhibitor + Meglitinides + SGLT2 inhibitor + Sulphonylurea + TZDs) + metformin	Phase 4	<ul style="list-style-type: none"> • A number of subjects who achieve HbA(1c) below or equal to 6.5% (48 mmol/mol). • A number of subjects who achieve HbA(1c) below or equal to 7.0% (53 mmol/mol) without weight gain. • Changes from baseline in FPG and body weight gain. 	[51]

(continued on next page)

Table 1 (continued)

Clinical Trial No.	Population Size	Status	Interventions	Phase	End Point	Reference
NCT00006305	2368	Completed	1, 2. Revascularization with intensive medical therapy (1. Insulin, sulfonylurea; 2. Biguanides, TZDs) along with ACEIs, ARBs, beta-blockers and CCBs) 3, 4. Intensive medical therapy with delayed revascularization (3. Insulin, sulfonylurea, and 4. Biguanides, TZDs) along with ACEIs, ARBs, beta-blockers and CCBs.	Phase 3	<ul style="list-style-type: none"> • The baseline health status was improved significantly at 1-year in the treatment group. • Compared with medical therapy, revascularization was associated with significant improvement in the Duke Activity Status Index and was maintained over a 4-year follow-up. • Duke Activity Status Index was significantly larger in the patients intended for coronary artery bypass surgery than in the patients intended for percutaneous coronary intervention. 	[57]
NCT00575874	150	Completed	1, 2 and 3. Rivoglitazone HCl (0.5, 1.0, and 1.5 mg, respectively) 4. Pioglitazone HCl 5. Placebo	Phase 2	<ul style="list-style-type: none"> • Change from baseline in HbA(1c) for rivoglitazone HCl vs. placebo. • Change from baseline in FPG for rivoglitazone HCl vs. placebo. • Change from baseline in HbA(1c) for pioglitazone HCl. 	[53]
NCT00549874	27	Completed	1. Rosiglitazone 2. Glyburide	NA	<ul style="list-style-type: none"> • Rosiglitazone significantly reduced plasma nitrotyrosine, hs-CRP, and von Willebrand antigen and significantly increased plasma adiponectin but no significant changes in these parameters were observed with glyburide. • Significant deterioration in both resting and stress myocardial blood flow in the glyburide group but not in the rosiglitazone group. 	[54]
NCT02231021	216	Completed	1. Alogliptin 2. Pioglitazone 3. Alogliptin + pioglitazone	Phase 4	<ul style="list-style-type: none"> • Change from baseline in HbA(1c), glycated albumin, GA/HbA(1c) ratio, FPG, HOMA-IR, PAI, hs-CRP, BNP, TC, and TGs. • Incidence of hyperglycemia rescue. • Proportion of subjects achieving HbA(1c) < 7.0 and 6.5%. • A number of hypoglycemic event rates. • A number of subjects with adverse events of special interest. 	[55]
NCT01001611	173	Completed	1. CKD-501 (Lobeglitazone) (0.5 mg) 2. Placebo	Phase 3	<ul style="list-style-type: none"> • HbA(1c) < 7% was achieved significantly more in the lobeglitazone group. • Lobeglitazone treatment significantly improved markers of insulin resistance, TGs, HDL cholesterol, small dense LDL cholesterol, FFA, and apolipoprotein B/CIII levels. • More weight gain was in the lobeglitazone group than in the placebo. 	[56]

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; AUC: area under curve; BMI: body mass index; BNP: brain natriuretic peptide; CCBs: calcium channel blocker; CPP: cerebral perfusion pressure; DTSQ: diabetes treatment satisfaction questionnaire; DPP: dipeptidyl peptidase; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; FBS: fasting blood sugar; FPG: fasting plasma glucose; FRK: fractalkine; FFA: free fatty acid; GLP-1: glucagon-like peptide 1; GA: glycated albumin; HbA(1c): glycated hemoglobin; HDL: high-density lipoproteins; hs-CRP: high sensitivity C-reactive protein; HOMA: homeostatic model assessment; IR: insulin resistance; IL: interleukin; LDL: low-density lipoproteins; MRE: magnetic resonance elastography; MRF: magnetic resonance fingerprinting; MRI-PDFF: magnetic resonance imaging proton density fat fraction; MCP-1: monocyte chemoattractant protein-1; MI: myocardial infarction; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NA: not applicable; PAI: plasminogen activator inhibitor; SMBG: self-monitoring of blood glucose; SNPs: single nucleotide polymorphisms; SGLT-2: sodium-glucose cotransporter-2; TC: total cholesterol; TACE: trans arterial chemoembolization; TEAE: treatment-emergent adverse events; TGs: triglycerides.



Fig. 3A. General structure of PPAR (modified and), adapted from [64].

Table 2
Isoforms of PPAR.

Isoforms	Location	Biological Functions	Agonists
PPAR-α	Hepatocytes, cardiomyocytes, kidney cortex, skeletal muscles, and enterocytes	Fatty acid oxidation, mainly in the liver and heart and to a lesser extent in muscles. Reduces inflammation both in the vascular wall and the liver. Regulates energy homeostasis.	Unsaturated fatty acids, 8-(S) hydroxyl eicosatetraenoic acid, fibrates (clofibrate, fenofibrate, and bezafibrate), B4 leucotriene, prostaglandin E, or farnesol
PPAR-δ/β	In almost all the tissues, mainly higher levels in the brain, adipose tissue, and skin	Regulator of fat oxidation, lipoprotein metabolism, glucose homeostasis. Regulates the genes involved in adipogenesis, cholesterol metabolism, inflammation, and atherosclerosis.	Fatty acids
PPAR-γ	White and brown adipose tissue (major) Immune cells (monocytes, macrophages, and Peyer's patches in the digestive tract), mucosa of the colon and cecum and in the placenta (lesser extent).	Insulin sensitization, adipogenesis, and adipocyte differentiation, inflammation, and cell growth	TZDs, unsaturated fatty acids such as oleate, linoleate, eicosapentaenoic, and arachidonic acids, and prostanoid.

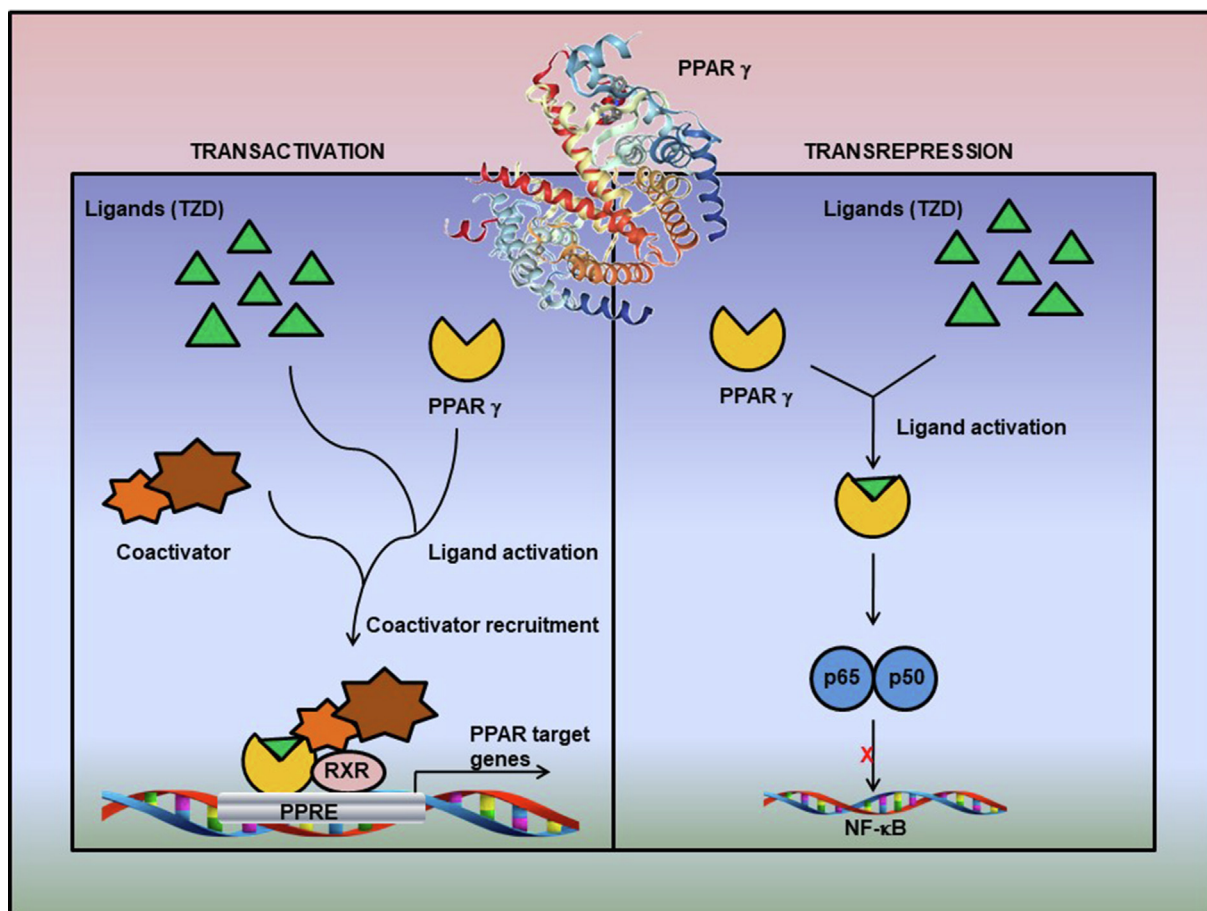


Fig. 3B. Mechanistic action of TZDs (modified and), adapted from [68].

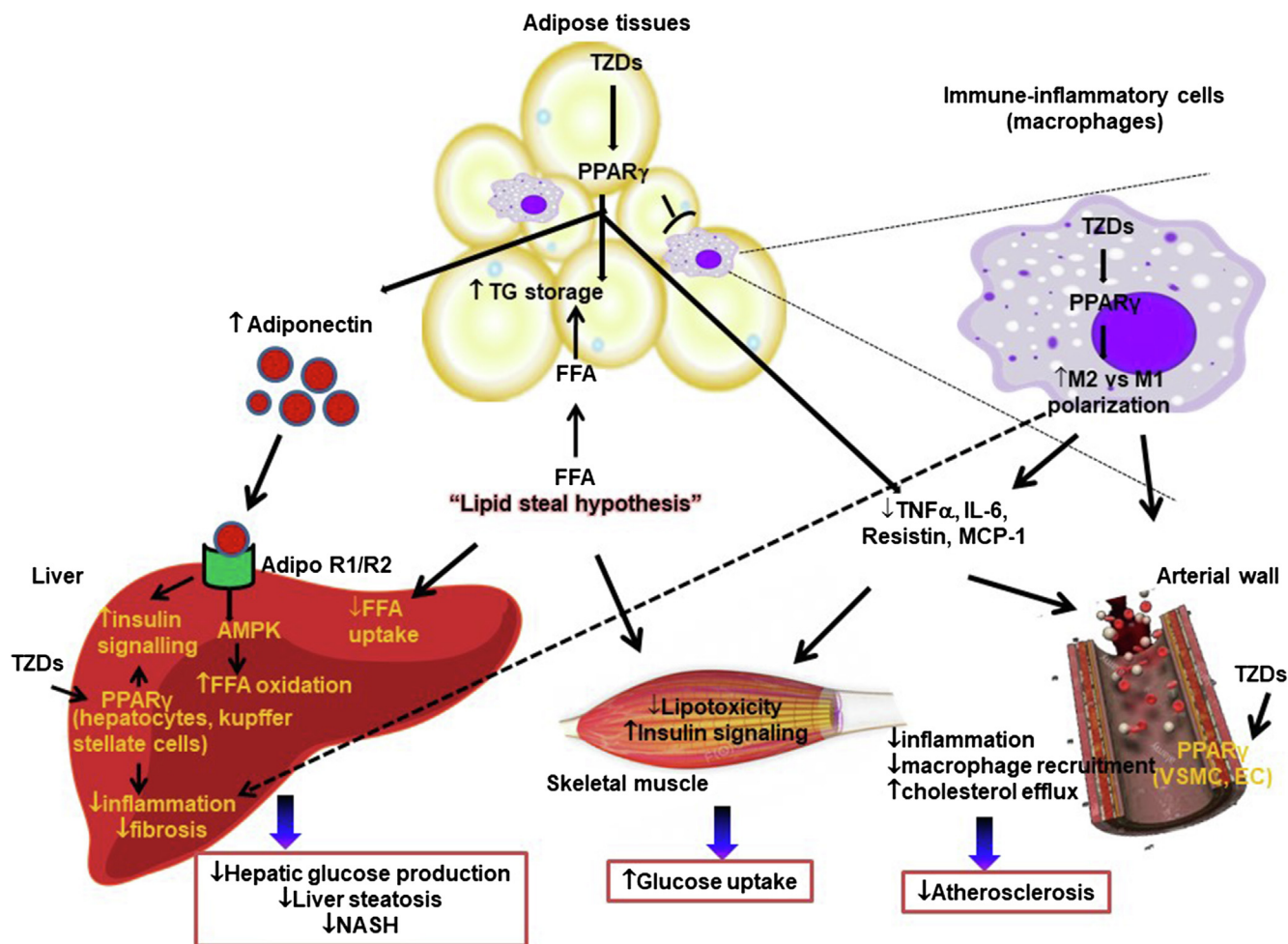


Fig. 4. Various targets of TZDs on PPAR- γ (modified and), adapted from [69].

thereby regulating various inflammatory mediators such as cytokines, leukocyte, etc. (Fig. 3B) [66,68].

In adipose tissues, when PPAR- γ gets activated by TZDs, it causes lipid uptake and triglycerides (TGs) storage. Free fatty acids (FFAs) are further taken up by white adipose tissues (WAT) and sequestered away from tissues (liver, skeletal muscle) where their growth leads to obstruction of insulin signaling called as lipid steal hypothesis. PPAR- γ also controls the adipocyte production from various signaling molecules like adipokines. PPAR- γ also gets directly activated by TZDs in macrophages which cause an anti-inflammatory M2 phenotype and thereby, decrease macrophage infiltration in WAT. TZDs also act on PPAR- γ in the parenchymal cells of steatosis liver or in Kupffer and stellate cells which cause a reduction in fibrosis and inflammation. TZDs also play a role in atherosclerosis by interfering with PPAR- γ action in macrophages [Fig. 4] [69].

Chemistry and pharmacological profile of TZD derivatives

Alkoxy benzyl TZDs derivatives

5-(4-Pyridylalkoxybenzylidene)-2,4-TZDs (**8**) analogs of pioglitazone were synthesized by Momose et al. through Knoevenagel condensation of aldehydes (**7**) with the corresponding thiazolidine-2,4-diones as shown in **S2**. The aldehydes (**7**) were synthesized from the coupling of pyridylethanol (**4**) with

4-fluorobenzonitrile to give 4-(2-(2-Pyridyl)ethoxy)benzonnitriles (**5**) followed by either treatment with Raney Ni in HCO_2H or with tosylchloride and 4-hydroxybenzaldehyde (**6**) in presence of phase transfer catalyst to give aldehydes (**7**). All the analogs were then evaluated for hypoglycemic and hypolipidemic activity in KKA^Y mice by administering as dietary admixture at a concentration of 0.005% or 0.01% for 4 days. The compound **8a-d** reduced blood glucose level (38–48%) and plasma TG level (24–58%) and the effect was found to be equipotent to pioglitazone (Table 4) [70].

Sohda et al. prepared a series of 5-(4-(2- or 4-azolyalkoxy)benzyl- or -benzylidene)-2,4-TZDs by using **S3** in which Meerwein arylation of aniline derivatives (**9**) give the 3-aryl-2-bromopropionates (**10**), which were further reacted with thiourea (**1**) to give iminothiazolidinones (**11**) followed by acid hydrolysis of **11** give the resulted product (**12**). The synthesized compounds were evaluated for hypoglycemic and hypolipidemic activities in genetically obese and diabetic KKA^Y mice. The compounds were administered along with food as a dietary admixture at 0.005 or 0.001%. Among the compounds synthesized, 5-(4-(2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy)-benzyl)-2,4-TZD (**12**) exhibited the most potent activity (>100 times) than that of pioglitazone (Table 4) [71].

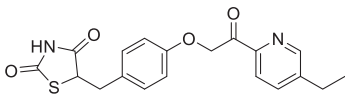
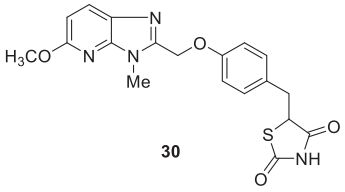
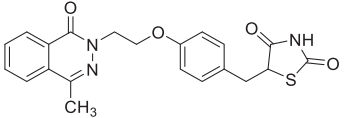
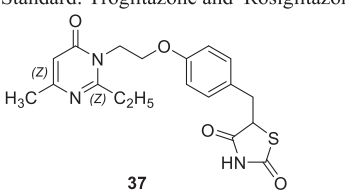
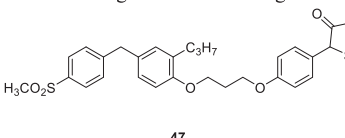
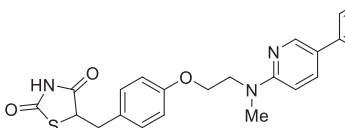
Tanis et al. have reported the synthesis of pioglitazone metabolites (**15** and **16**) by oxidizing pioglitazone (**13**) using *m*-chloroperoxybenzoic acid (*m*CPBA) to give *N*-oxide (**14**), which was then converted to alcoholic derivative (**15**) of pioglitazone

using trifluoroacetic anhydride (TFAA) in methylene chloride which in turn upon oxidation gives putative metabolite (**16**) as shown in **S4**. The antihyperglycemic activity of these metabolites was determined in the KKA^y mice in comparison to pioglitazone. The compounds were administered as a food admixture at a dose of 100 mg/kg for 4 days. The antihyperglycemic activity was determined from the ratio of glucose level for the treated over the control group (T/C). As a result, compound **16** has proven to be the most potent of these metabolites with a T/C value of 0.39 in comparison to pioglitazone (T/C = 0.49). Further, the compounds were evaluated for their ability to augment insulin-stimulated lipogenesis *in vitro* in 3T3-L1 cells. Again, compound **16** was proven to be effective in augmenting insulin-stimulated lipogenesis through its ability to provide high levels of [¹⁴C] acetate incorpora-

tion into lipids at different concentrations (1, 3 and 10 μM), while others were roughly equivalent to pioglitazone. These results implicate that compound **16** is considered as a congener of pioglitazone with greater potency elicited through the simpler metabolic pathway (Table 3 and 4) [72].

Lohray et al. have reported the synthesis of a series of [(heterocycl)ethoxy]-benzyl]-2,4-TZDs (**19**) by the Knoevenagel condensation of aldehyde (17) and 2,4-TZD (3) in the presence of piperidinium benzoate to give benzylidenes (18) followed by catalytic reduction over Pd-C as shown in **S5**. Synthesized compounds were evaluated for antihyperglycemic and hypolipidemic activity and the effects were compared with troglitazone and rosiglitazone (BRL-49653) in *db/db* and *ob/ob* mice. The compound DRF-2189 (**18**) at 200 mg/kg have been shown to exhibit superior activity

Table 3
Summary of *in vitro* studies of TZDs on diabetes mellitus.

Compound	Cell line	Dose	IC ₅₀ /EC ₅₀	Effect	References
 16	3T3-L1 cells	0–10 μM		Stimulated insulin-mediated lipogenesis (via ¹⁴ C-acetate incorporation). Comparable activity at 10 μM to that of pioglitazone.	[72]
Standard: Pioglitazone					
 30	3T3-L1 cells	0.1% v/v		Increased adipocyte differentiation which is expressed as concentrations equivalent to the [¹⁴ C] uptake counts (0.080 μM).	[75]
Standard: Rosiglitazone					
 34	HEK 293T cells	0.25, 0.5, 1.0, 5.0 μM		Increased PPAR-γ transactivation in a dose-dependent manner (11 folds) in comparison to troglitazone (5.5 folds) and pioglitazone (6 folds).	[76]
Standard: Troglitazone and Rosiglitazone					
 37	HEK 293T cells	0.010, 0.050, 0.2, 1.0 and 5.0 μM		Increased PPAR-γ transactivation in a dose dependent manner (20 folds) in comparison to rosiglitazone (19 folds) and pioglitazone (6 folds)	[77]
Standard: Pioglitazone and Rosiglitazone					
 47	COS-1 cells	–	EC ₅₀ = 0.12 μM IC ₅₀ = 0.25 μM	Increased PPAR-γ activation (10-fold) than standard	[80]
Standard: Rosiglitazone					
 53	3T3-L1 cells	3 × 10 ⁻⁵ – 3 × 10 ⁻¹¹ M	EC ₅₀ = 0.00054 μM	Better TG accumulation activity was observed in comparison to rosiglitazone (0.047 μM) and pioglitazone (0.015 μM)	[81]
Standard: Pioglitazone and Rosiglitazone					

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Table 3 (continued)

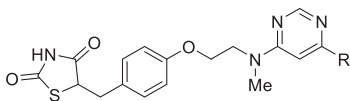
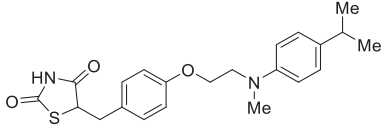
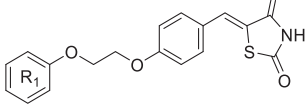
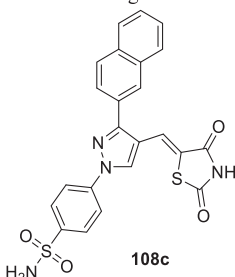
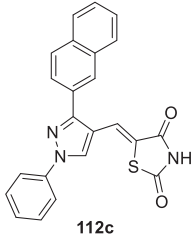
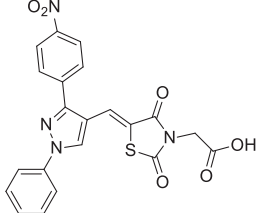
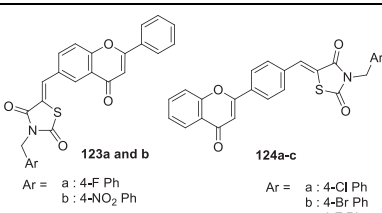
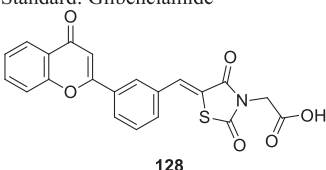
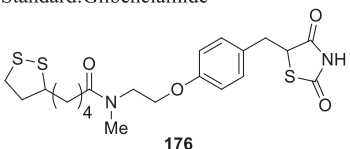
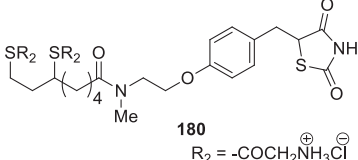
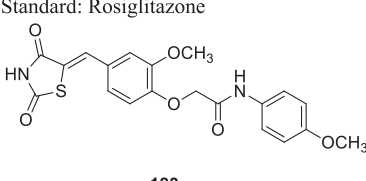
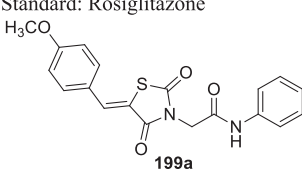
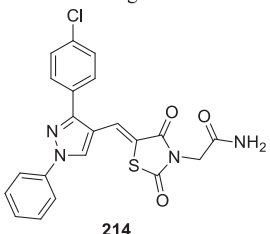
Compound	Cell line	Dose	IC ₅₀ /EC ₅₀	Effect	References
 <p>63a and b a : R = phenoxy b : R = <i>p</i>-methoxy phenoxy</p>	3T3-L1 cells	3×10^{-5} – 3×10^{-11} M	EC ₅₀ = 0.0012 μ M (63a) and 0.00041 μ M (63b)	Better TGs accumulation activity was observed in comparison to rosiglitazone (0.047 μ M) and pioglitazone (0.015 μ M)	[83]
<p>Standard: Pioglitazone and Rosiglitazone</p>  <p>66</p>	1) CV1-cells 2) Murine macrophage cell line	2 μ M 100 μ L		Marginal PPAR- γ transactivation (21.2%) with no PPAR- α activity Inhibits NO production (51.5%)	[84]
<p>Standard: GW409544 and KRP-297</p>  <p>73a R₁ : 2,4-Cl</p>	1) Rat hemi-diaphragm 2) HEp-2 and A549 cells	2 mg 100 μ L	CTC ₅₀ is 80 μ g/mL against HEp2 cells and no activity against A549 cells	Enhanced glucose uptake activity especially in the presence of insulin (38.0 mg/dL/45 min) Showed significant cytotoxic activity	[86]
<p>Standard: Rosiglitazone</p>  <p>108c</p>	1) HEK 293 cells 2) 3T3-L1 cells	10 μ M 10 μ M		Increased PPAR- γ transactivation (61.2%) as compared to standard Increased expression of PPAR- γ significantly due to AMPK activation (1.9 folds)	[89]
<p>Standard: Rosiglitazone and Pioglitazone</p>  <p>112c</p>	1) HEK 293 cells 2) 3T3-L1 cells	10 μ M 10 μ M		Increased PPAR- γ transactivation (52.06%) as compared to standard Increased expression of PPAR- γ significantly due to AMPK activation (2.35-fold)	[91]
<p>Standard: Rosiglitazone and Pioglitazone</p>  <p>116b</p>	Alpha-amylase	10 mg	4.08 μ g/mL	Better alpha-amylase inhibitory activity than the standard acarbose (8 μ g/mL)	[92]
<p>Standard: Acarbose</p>					

Table 3 (continued)

Compound	Cell line	Dose	IC ₅₀ /EC ₅₀	Effect	References
 <p>123a and b Ar = a: 4-F Ph b: 4-NO₂ Ph</p> <p>124a-c Ar = a: 4-Cl Ph b: 4-Br Ph c: 4-F Ph</p>	INS-1 cells	1 and 10 µg/mL		Increased insulin release at higher concentration	[94]
<p>Standard: Glibenclamide</p>  <p>128</p>	1) INS-1 cells 2) Aldose reductase enzyme	1 and 10 µg/mL 0.1 mL	0.415 µg/mL against Aldose reductase	More insulintropic effect (128.6%) at higher concentration (10 µg/mL) Showed the highest aldose reductase inhibitory activity (86.57%)	[95]
<p>Standard: Glibenclamide</p>  <p>176</p>	3T3-L1 cells	0.1, 1.0 and 10 µM		Caused differentiation of 3T3-L1 preadipocyte fibroblasts into myoblast during terminal differentiation and increased lipid accumulation	[100]
 <p>180 R₂ = -COCH₂NH₃⁺Cl⁻</p>					
<p>Standard: Rosiglitazone</p>  <p>183</p>	Rat hemidiaphragm	2 mg		Enhance the glucose uptake (36.25 mg/g/45 min)	[101]
<p>Standard: Rosiglitazone</p>  <p>199a</p>	Rat hemidiaphragm	1 and 2 mg		Significant glucose uptake activity especially in the presence of insulin (42.16 mg/dL)	[102]
<p>Standard: Rosiglitazone</p>  <p>214</p>	1) HEK 293 cells 2) 3T3-L1 cells	10 µM 10 µM		Increased PPAR-γ transactivation (53.67%) as compared to standard Increased expression of PPAR-γ significantly due to AMPK activation (2.1 folds)	[106]
Standard: Pioglitazone and Rosiglitazone					

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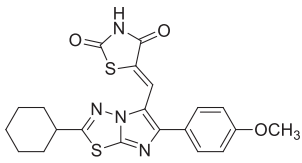
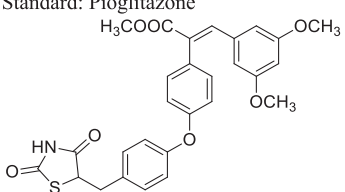
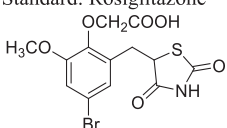
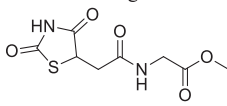
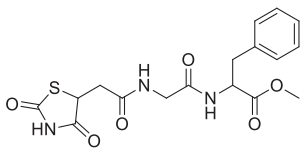
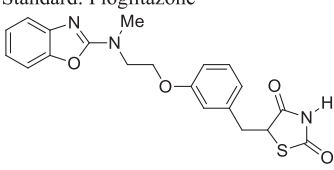
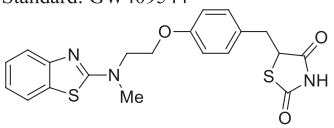
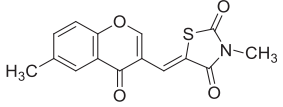
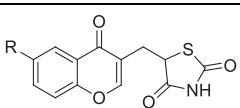
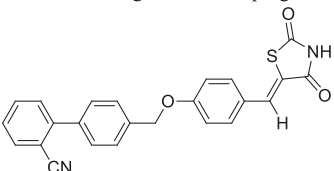
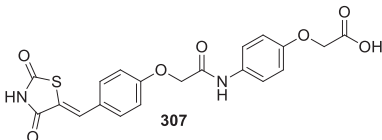
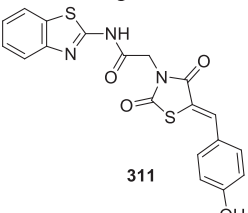
Compound	Cell line	Dose	IC ₅₀ /EC ₅₀	Effect	References
 219b	NIH3T3 cells	Different concentrations	EC ₅₀ = 280 nM	Significant PPAR- γ agonistic activity with 64% activation	[107]
Standard: Pioglitazone  232	HEK 293 cells	Between 0.1 and 30	EC ₅₀ = 0.284 μ M	Moderate PPAR- γ agonist activity	[109]
Standard: Rosiglitazone  237b	HEK 293 cells 3T3-L1 cells	10 μ M 10 μ M	EC ₅₀ = 0.77 μ M	Increased PPAR- γ transactivation (48.35, 54.21%) but found to be PPAR- α and PPAR- δ inactive Increased expression of PPAR- γ significantly due to AMPK activation (2.0 folds)	[110]
Standard: Rosiglitazone and Pioglitazone  242	Yeast cells	10, 20, 40, 80, 100 and 200 μ L/mL		Increased glucose uptake by the cells (39.23 and 38.19%)	[111]
 243					
Standard: Pioglitazone  278	CV-1 cells	–		Significant PPAR- γ activity (113.2%) without any PPAR α activity.	[119]
Standard: GW409544  287	1) CV-1 cells 2) RAW 264.7 cells	2 μ M 5, 10 and 20 μ M		Significant PPAR- γ activity (120%) without any PPAR α activity Inhibitory activity against NO production	[121]
Standard: GW409544  294	INS-1 cells	0.001 and 0.01 mg/mL		Increase the insulin release at lower concentration (120%) but more potent at higher concentration (152%)	[123]
Standard : Glibenclamide					

Table 3 (continued)

Compound	Cell line	Dose	IC ₅₀ /EC ₅₀	Effect	References
 298b R : Cl	1) hERG 2) 3T3-L1 cells	– 10 μM		No cardiotoxic effect (135 μM) Increased PPAR-γ gene expression due to the activation of AMPK (45%)	[124]
Standard : Rosiglitazone and pioglitazone					
 301	3T3-L1 cells	–	0.58 μM (hERG)	Significantly increased the levels of PPAR-γ, PPAR-α and GLUT4	[125]
 307	3T3-L1 cells	10 μM	0.01 μM (hERG)	Increased the relative expression of PPAR-γ and GLUT-4 (2-folds) but no change was observed in the expression of PPAR-α	[126]
Standard: Pioglitazone and fenofibrate					
 311	PTP1B	20 μM	3.7 μM	The decrease in enzyme activity up to 85%	[127]

AMPK: adenosine monophosphate-activated protein kinase; EC: effective concentration; GLUT4: glucose transporter type 4; HEK cells: human embryonic kidney cells; HEP-2: human epithelial type 2 cells; INS-1 cells: insulin-secreting cell; NO: nitric oxide; PPAR: peroxisome proliferator-activated receptors; PTP1B: protein-tyrosine phosphatase 1B; TGs: triglycerides.

in terms of blood glucose (74%) and TG (77%) reduction than those in troglitazone (200 mg/kg) treated (24 and 50%, respectively) mice. Then, the efficacy of compound DRF-2189 (**18**) was compared with rosiglitazone in *db/db* mice. Compound DRF-2189 (**18**) at 10 and 100 mg/kg have shown to reduce plasma glucose whereas, rosiglitazone failed to show the activity at 10 mg/kg dose. Further, dose–response effects of DRF-2189 (**18**) (1, 3, 10 mg/kg) were carried out along with rosiglitazone (1, 3, 10 mg/kg) and troglitazone (100, 200 and 800 mg/kg). Both DRF-2189 (**18**) and rosiglitazone were shown to exhibit equipotent activity in reducing plasma glucose but troglitazone failed to show the activity even at a higher dose. In addition, compound DRF-2189 (**18**) and rosiglitazone failed to show the activity on the reduction of TG; however, compound DRF-2189 (**18**) at 3 and 10 mg/kg has been shown to reduce total cholesterol. In addition, both DRF-2189 and rosiglitazone have been shown to exhibit equipotency in oral glucose tolerance test (OGTT) after 9-days of treatment in *db/db* mice. Consequently, both the drugs were evaluated in *ob/ob* mice at 10 mg/kg for 14 days. The reduction in blood glucose level (51–59%) and TG levels (53–55%) were observed and the results were in accordance with *db/db* study. The indole analog DRF-2189 (**18**) was found to be a very potent insulin sensitizer, comparable to rosiglitazone in genetically induced diabetic models (i.e., *ob/ob* and *db/db* mice) (Table 4) [73].

Lohray et al. synthesized a series of substituted pyridyl and quinoliny containing 2,4-TZDs incorporated with an interesting cyclic amine as shown in **S6**. The aldehyde (20) underwent Knoevenagel condensation with TZD (3) to afford benzylidene derivatives

(21) followed by reduction yielded final derivatives (**22a and b**). The synthesized compounds were evaluated for euglycemic and hypolipidemic effects in *db/db* mice by administering the synthesized derivatives at a dose of 100 mg/kg for 6 days. The compounds synthesized were then compared with unsaturated rosiglitazone. As a result, compound **22a** showed very good euglycemic and hypolipidemic activities measured in terms of percentage reduction in plasma glucose (57%) and TG (77.75%) level in comparison to unsaturated rosiglitazone (55% and 35%, respectively). On the other hand, quinoline based compound (**22b**) also had significantly shown to reduce plasma glucose than rosiglitazone, but failed to produce a significant result on plasma TG. Further, their saturated derivatives were prepared and evaluated in the same diabetic model at a dose of 30 mg/kg for 6 days in comparison to saturated rosiglitazone (BRL-49653). The results showed that the euglycemic and hypolipidemic activity were maintained for a saturated analog of compound **22a** (52% plasma glucose reduction) similar to unsaturated analog. Surprisingly, quinoline based saturated analogs of TZD (**22b**) had shown to exhibit good hypolipemic activity in addition to euglycemic activity. Then, they prepared various salt (maleate, hydrochloride or sodium salt) forms of TZD and evaluated at 30 mg/kg for 6 days in the same animal model. It was found that HCl and maleate salt form of compound **22a** exhibited euglycemic (70% and 63.6%, respectively) and hypolipidemic (31% and 66.4%, respectively) activities. Further, dose-dependent studies were carried out in *db/db* and *ob/ob* mice at different doses of 3, 10, 30 mg/kg and 1, 3, 10 mg/kg, respectively for 14 days. The results in *db/db* mice revealed that maleate salts of compound **22a** (10 and

Table 4
Summary of *in vivo* studies of TZDs on diabetes mellitus.

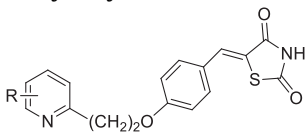
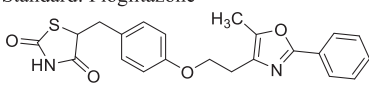
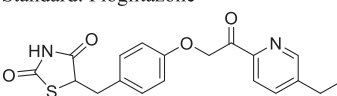
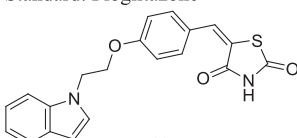
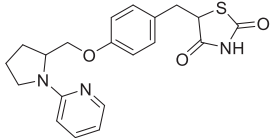
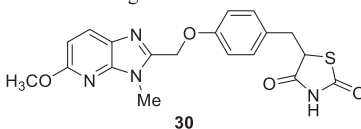
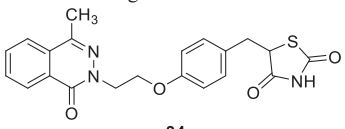
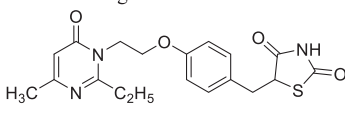
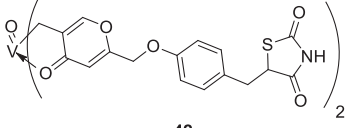
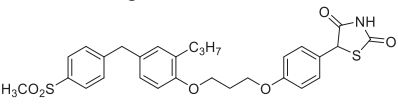
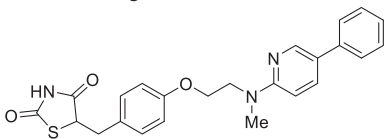
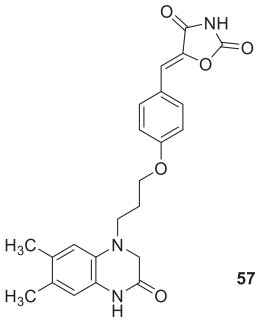
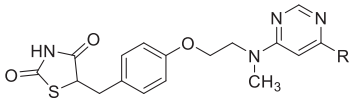
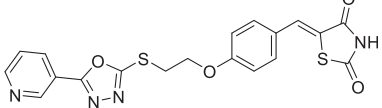
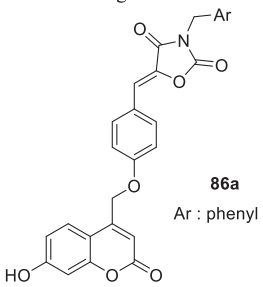
Compound	Cell line	Dose	Effect	References
<p>Alkoxy benzyl based TZDs</p>  <p>8a-d</p> <p>a : H b : 3-Me c : 6-Me d : 5-Et</p>	KKA ^y mice	0.005% or 0.01% as dietary admixture (4 days)	Reduction in BG (38–48%) and TG (24–58%)	[70]
<p>Standard: Pioglitazone</p>  <p>12</p>	KKA ^y mice	0.005% or 0.01% as dietary admixture (4 days)	Reduction of PG and TG 100 times more than pioglitazone	[71]
<p>Standard: Pioglitazone</p>  <p>16</p>	KKA ^y mice	100 mg/kg (4 days)	Reduction in BG (T/C = 0.39)	[72]
<p>Standard: Pioglitazone</p>  <p>18</p>	db/db mice ob/ob mice	200 mg/kg 10 and 100 mg/kg (9 days) 1,3 and 10 mg/kg (14 days)	Reduction in BG (74%) and TG (77%) Equipotent activity in reducing PG Reduction in PG (51–59%) but no reduction in TG	[73]
<p>Standard: Troglitazone and Rosiglitazone</p>  <p>22a</p>	db/db mice ob/ob mice	100 mg/kg (6 days) 1, 3, 10 and 30 mg/kg (14–15 days) 3, 10, 30 and 100 mg/kg (15 days)	Reduction in PG (57%) and TG (77.7%) Impressive improvement in glucose tolerance even at 10 mg/kg Dose-dependent reduction in PG	[74]
<p>Standard: Rosiglitazone</p>  <p>30</p>	KK mice	1 mg/kg (1 day) 50 mg/kg (2 weeks)	Reduction in BG (55.8%) and cardiac hypertrophy	[75]
<p>Standard: Rosiglitazone</p>  <p>34</p>	db/db mice Wistar rats	10 mg/kg (6 days) 100 mg/kg (14 days)	Reduction of PG (72%) and TG (68%) No significant change in body weight and food consumption	[76]
<p>Standard: Pioglitazone</p>  <p>37</p>	db/db mouse	30 or 100 mg/kg (6 days) 0.3, 3 and 10 mg/kg (15 days) 100 mg/kg (28 days)	Reduction in PG (73%) and TG (85%) Better than standard in terms of reduction in PG levels Neither mortality nor any evidence of toxicity	[77]
Standard: Rosiglitazone and pioglitazone				

Table 4 (continued)

Compound	Cell line	Dose	Effect	References
 42	STZ-diabetic rats	0.1 mmol/kg (3 days)	Reduction in BG (47%)	[78]
Standard: Rosiglitazone and BMOV				
 47	db/db mouse	5 and 10 mg/kg (11 days)	Dose-dependent reduction in glucose (86%) and TG (78%)	[80]
Standard: Rosiglitazone				
 53	KKAY mice	1, 6 and 30 mg/kg (5 days)	Reduction in BG and TG (ED ₂₅ = 0.020 and 2.5 mg/kg/day)	[81]
Standard: Rosiglitazone and pioglitazone				
 57	Wistar male rats	3, 10, 30 and 100 mg/kg (14–15 days)	Dose-dependent reduction in PG and TG	[82]
Standard: Rosiglitazone				
 63a and b a : R = phenoxy b : R = p-methoxy phenoxy	KKAY mice	1,6 and 30 mg/kg (5 days)	Drastically improved the hypoglycemic activity	[83]
Standard: Rosiglitazone and pioglitazone				
 70a	Alloxan-induced diabetic male Wistar rats	3,10,30 and 100 mg/kg (15 days)	Reduction of PG and TG	[85]
Standard: Pioglitazone				
 86a Ar : phenyl	STZ-induced diabetic Wistar rats	35 μmol/kg (15 days)	Reduction in PG (44.7%)	[87]
Standard: Rosiglitazone				

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Table 4 (continued)

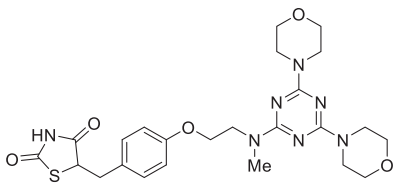
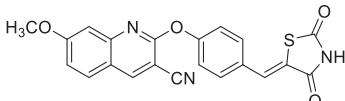
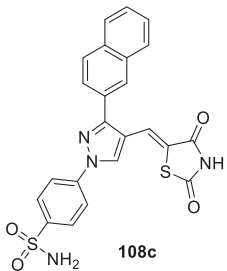
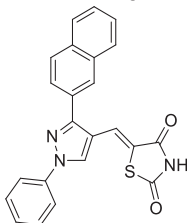
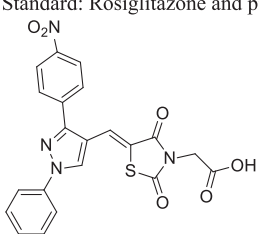
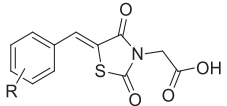
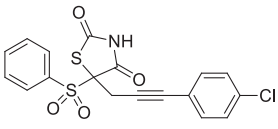
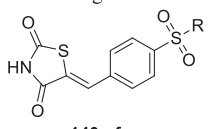
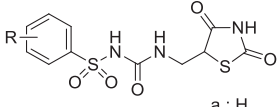
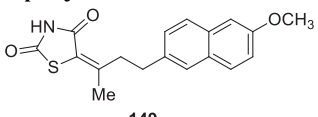
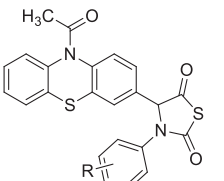
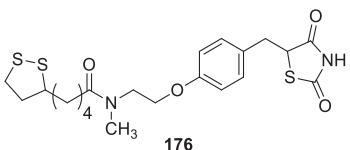
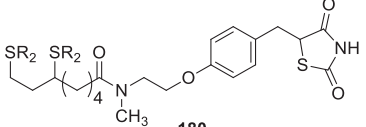
Compound	Cell line	Dose	Effect	References
 <p>94</p> <p>Standard: Rosiglitazone</p>	Alloxan-induced diabetic rat model	3 mg/kg (16 days)	Reduction in BG (295.50 mg/dL), enhancement in HDL level (3.16 mg/dL) and HDL/LDL ratio (4.02)	[10]
 <p>102</p> <p>Standard: Glibenclamide</p> <p>Pyrazole-based TZDs</p>	Sucrose loaded rat model	100 mg/kg (2 days)	9.4% improvement in oral glucose tolerance	[88]
 <p>108c</p>	STZ-induced diabetic rat model Hepatotoxicity study	36 mg/kg (15 days) 108 mg/kg	Reduction in BG (134.1 mg/dL) No bodyweight change Lower the levels of AST, ALT, and ALP and cause no damage to the liver	[89]
 <p>112c</p> <p>Standard: Rosiglitazone and pioglitazone</p>	STZ-induced diabetic rat model Hepatotoxicity study	36 mg/kg (15 days) 108 mg/kg	Reduction in BG (140.1 mg/dL) No bodyweight change Lower the levels of AST, ALT, and ALP and cause no damage to the liver	[91]
 <p>116b</p> <p>Standard: Rosiglitazone and pioglitazone</p>	C57BL/6J mice	30 mg/kg (15 days)	Compound 116b (134.46 mg/dL) exhibited significant blood glucose-lowering activity and were found to be similar to standard pioglitazone (136.56 mg/dL)	[92]
 <p>119a and b</p> <p>a : R = 3,4-OCH₃ b : R = 3,4,5-OCH₃</p> <p>Standard: Pioglitazone</p>	Sucrose loaded model	100 mg/kg (1 day)	Reduction in BG within 30 min and the effect was maintained till the duration of 120 min	[93]

Table 4 (continued)

Compound	Cell line	Dose	Effect	References
<p>Sulfonyl based TZDs</p>  <p>136</p>	<p><i>db/db</i> mice <i>ob/ob</i> mice Zucker rats</p>	<p>100 and 20 mg/kg (4 days) 100 mg/kg (4 days) 20 mg/kg (4 days)</p>	<p>Reduction in PG (52 and 21%) Reduction in glucose (40%) and insulin (65%) Significantly improved the glucose tolerance</p>	[96]
<p>Standard: Ciglitazone</p>  <p>140a-f</p> <p>R : various aromatic/ heterocyclic amines</p>	<p>Alloxan-induced diabetic albino rats</p>	<p>36 mg/kg (1 day)</p>	<p>Moderate reduction in BG (95–180 mg/dL)</p>	[4]
<p>Standard: Glibenclamide</p>  <p>147a-d</p> <p>a : H b : 4-Cl c : 2,4-Cl d : 2,5-Cl</p>	<p>Sucrose loaded rat model</p>	<p>100 mg/kg (1 day)</p>	<p>Significantly inhibited the postprandial rise in BG (14.3–17.2%)</p>	[97]
<p>Standard: Metformin</p> <p>Naphthyl based TZDs</p>  <p>149</p>	<p><i>db/db</i> mice</p>	<p>30 mg/kg (6 days)</p>	<p>Reduction in PG (16%) and TG (50%)</p>	[98]
<p>Standard: Troglitazone and MCC-555</p> <p>Phenothiazine based TZDs</p>  <p>169a and b</p> <p>a : 4-Cl b : 3,4-Cl</p>	<p>STZ-induced diabetic Wistar rats</p>	<p>5 and 10 mg/kg (21 days)</p>	<p>Stimulates insulin secretion by inhibiting K⁺ATP channels</p>	[99]
<p>Standard: Rosiglitazone</p> <p>Amide-based TZDs</p>  <p>176</p>	<p><i>fa/fa</i> Zucker rats</p>	<p>100 mg/kg (4 weeks)</p>	<p>No effect on BG and body weight but a marked reduction in serum insulin (78%) and TG (83%)</p>	[100]
 <p>180</p> <p>R₂ = -COCH₂NH₂·HCl</p>	<p>Standard: Rosiglitazone</p>			

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Table 4 (continued)

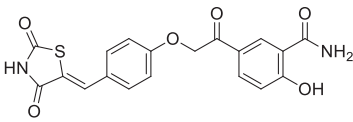
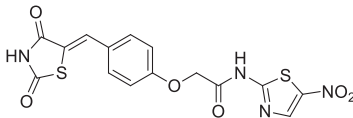
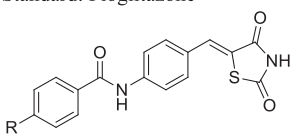
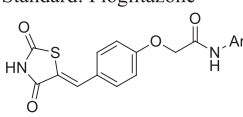
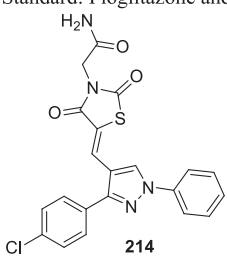
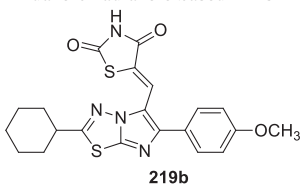
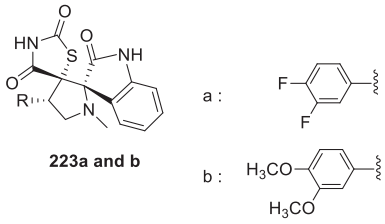
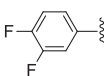
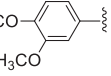
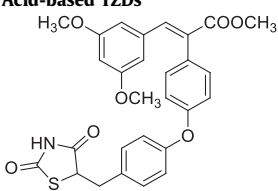
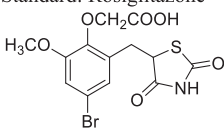
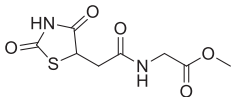
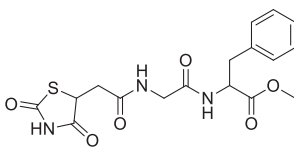
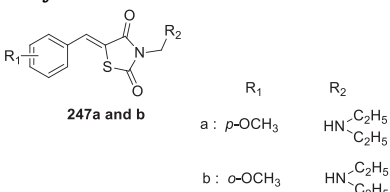
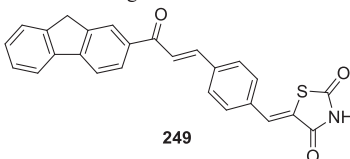
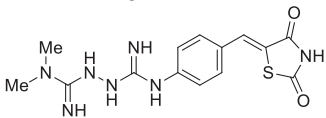
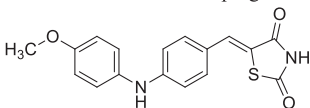
Compound	Cell line	Dose	Effect	References
 <p>202</p>	STZ-induced diabetic rat model	20 mg/kg (14 days)	Reduction in BG (64% and 56%) and TG (74% and 78%)	[103]
 <p>205</p>				
<p>Standard: Pioglitazone</p>  <p>209a and b a : CH₂Cl b : CH₂CH₃</p>	Albino Rats STZ- NA induced diabetic rat model	100 and 500 mg/kg (14 days) 10 and 100 mg/kg (14 days)	Well tolerated up to higher dose and cause no mortality Reduction in PG (271 and 304 mg/dL) and TG (97 and 94 mg/dL)	[104]
<p>Standard: Pioglitazone</p>  <p>212a Ar : 2-methoxyaniline</p>	DMS-induced Wistar albino mice	30 mg/kg (7 days)	Reduction in PG (113.7 mg/dL)	[105]
<p>Standard: Pioglitazone and metformin</p>  <p>214</p>	STZ-induced diabetic rat model Hepatotoxicity study	36 mg/kg (15 days) 108 mg/kg	Reduction in BG (142.4 mg/dL) No body weight change Lower the levels of AST, ALT, and ALP and cause no damage to the liver	[106]
<p>Standard: Rosiglitazone and pioglitazone</p> <p>Imidazo-thiadiazole based TZDs</p>  <p>219b</p>	Alloxan-induced diabetic Wistar rats	3, 10, 30 and 100 mg/kg (15 days)	Dose dependent reduction in PG (40, 44, 59 and 73%) and TG (36, 35, 38 and 44%)	[107]
<p>Standard: Pioglitazone</p> <p>Dispiropyrrolidines based TZDs</p>  <p>223a and b a :  b : </p>	Alloxan-induced diabetic Wistar rats	36 mg/kg (3 days)	Reduction in BG (115.3 and 115.8 mg/dl)	[108]
<p>Standard: Rosiglitazone</p>				

Table 4 (continued)

Compound	Cell line	Dose	Effect	References
Acid-based TZDs  232	<i>ob/ob</i> mice	10 mg/kg (6 days) 3.1, 6.3 and 12.5 mg/kg (19 days) 5 mg/kg (11 days)	Reduction in BG (29%) All dose levels were effective in reducing BG No difference in body weight	[109]
Standard: Rosiglitazone  237b	STZ-induced diabetic rat model Hepatotoxicity study	36 mg/kg (15 days) 108 mg/kg	Reduction in BG (158.8 mg/dL) No bodyweight change Lower the levels of AST, ALT, and ALP and cause no damage to the liver	[110]
Standard: Rosiglitazone and pioglitazone  242	STZ-NA induced diabetic rats	30 mg/kg (14 days)	Reduction in PG (142 and 144.4 mg/dL)	[111]
 243				
Standard: Pioglitazone Benzylidene based TZDs  247a and b a: <i>p</i> -OCH ₃ R ₂ : HN-C ₂ H ₅ b: <i>o</i> -OCH ₃ HN-C ₂ H ₅	DMS-induced diabetic rat	50 mg/kg (5 days)	Reduction in BG level (58 and 65%)	[112]
Standard: Rosiglitazone  249	STZ-NA induced diabetic rat model	10, 30 and 50 mg/kg (1 day)	Dose-dependent reduction in BG was observed (39.83%, 44.62%, and 52.81%)	[113]
Standard: Rosiglitazone  252	Wistar rats Alloxan-induced diabetic rats	30 and 100 mg/kg (2 days) 100 mg/kg (14 days)	No change in weight without toxic effects Reduction in BG (65%)	[114]
Standard: Metformin and pioglitazone  254a	Albino Wistar rats (oral glucose tolerance test)	30 mg/kg (1 day)	Exhibited potent antidiabetic activity (100–120 mg/dL) similar to pioglitazone (100 mg/dL)	[115]

(continued on next page)

Table 4 (continued)

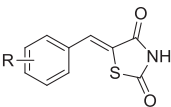
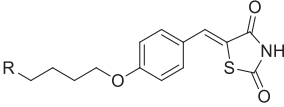


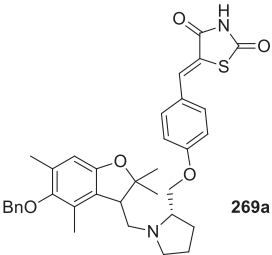
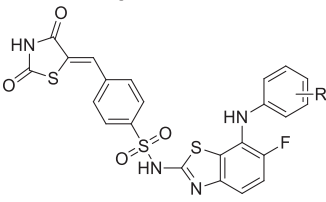
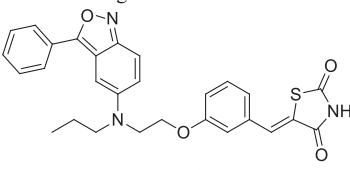
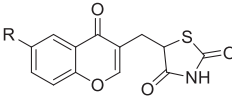
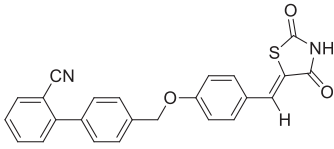
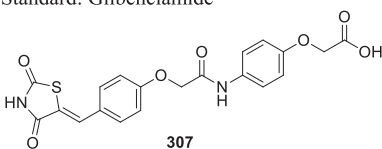
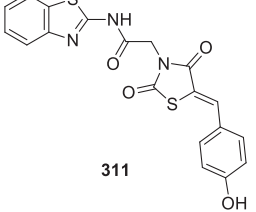
Compound	Cell line	Dose	Effect	References
 <p>256a and b a : 2-OH b : 3-Cl, 2-F</p>	Albino Wistar rats	175, 350, 700, 1400 and 2000 mg/kg (14 days)	Normal behavior and no physical changes were seen Fat deposits at a dose \geq 350 mg/kg	[116]
 <p>260a and b a :  b : </p>	DMS-induced diabetic mice	0.72 mg/kg (10 days)	An unexpected decrease in BG level within 30 min and then decreased steadily	[117]
Standard: Rosiglitazone				
Benzo-fused TZDs				
 <p>269a</p>	<i>db/db</i> mice	100 mg/kg (6 days)	Reduction in PG (66%) and TG (52%)	[118]
Standard: Troglitazone				
 <p>283a-c a : H b : <i>m</i>-NO₂ c : <i>p</i>-COOH</p>	Alloxan-induced diabetic albino rats	36 mg/kg (1 day)	Reduction in BG (116–123 mg/dL)	[120]
Standard: Troglitazone				
 <p>291</p>	Alloxan-induced diabetic mice	30 mg/kg (1 day)	Reduction in serum glucose level (–30.62%)	[122]
Standard: Rosiglitazone				
Chromones based TZDs				
 <p>298b R : Cl</p>	STZ-induced diabetic rats	15 days Hepatotoxicity study	Reduction in BG (135.5%), no change in body weight Lower levels of AST, ALT, and ALP without causing any hepatotoxicity	[124]
Standard: Rosiglitazone and pioglitazone				

Table 4 (continued)

Compound	Cell line	Dose	Effect	References
<p>Miscellaneous</p>  <p>301</p>	STZ-NA induced diabetic rats	50 mg/kg body weight	Decreased 32.36% glycemia level whereas glibenclamide reduced 43.6% levels	[125]
<p>Standard: Glibenclamide</p>  <p>307</p>	STZ-NA induced diabetic rats	50 mg/kg body weight	Decreased 31% glycemia level whereas glibenclamide reduced 43.6% levels	[126]
<p>Standard: Glibenclamide</p>  <p>311</p>	STZ-NA induced diabetic rats	50 mg/kg body weight	Decreased 34% glycemia level whereas glibenclamide reduced 43.6% levels	[127]

Standard: Glibenclamide

K⁺ATP: adenosine triphosphate-sensitive potassium channel; ALT: alanine transaminase; ALP: alkaline phosphatase; AST: aspartate transaminase; BG: blood glucose; DMS: dexamethasone; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NA: nicotinamide; PG: plasma glucose; STZ: streptozotocin; TG: triglycerides; T/C: treated group over control group.

30 mg/kg) were equipotent to rosiglitazone in terms of euglycemic activity but superior to rosiglitazone in terms of hypolipidemic activity at higher doses. The maleate salt of compound **22a** also exhibited excellent plasma glucose and TG lowering activities in *ob/ob* mice. The OGTT was also performed in both models (*db/db* and *ob/ob*). Maleate salt of unsaturated compound **22a** had shown an impressive improvement in glucose tolerance (10 mg/kg). In order to understand the mechanism, PPAR- γ (0.1, 1.0 and 10 μ M) and PPAR- α (50 μ M) transactivation assay was performed at different concentrations. The maleate form of unsaturated compound **22a** did not show any significant PPAR- γ or PPAR- α transactivation (Table 4) [74].

Oguchi et al. reported a series of imidazopyridine TZDs and synthesized them from their corresponding pyridines. 2,6-dichloro-3-nitropyridine (**23**) was substituted with methylamine to give 6-chloro-2-methylamino-3-nitropyridine (**24**) and was then reacted with sodium alkoxide to give **25**, which then reduced to give amino derivative (**26**). Imidazopyridine (**27**) was obtained through cyclization of **26** with glycolic acid followed by reaction with **28** gave compound **29** and the final product (**30**) was then obtained by removing trityl group (**S7**). The synthesized compounds were evaluated for its hypoglycemic activities, both *in vitro* and *in vivo*. The *in vitro* adipocyte differentiation activity of synthesized derivatives was carried out in the preadipocyte cell line (3T3-L1) at the concentration of 0.1% (v/v). The *in vivo* activity was carried out in KK mice for one day and one week by administering test compounds at a dose of 1 mg/kg and administering along with food as an admixture, respectively. Further, toxicity studies were also carried out for 2-weeks at a dose of 50 mg/kg. On the basis of evaluation, firstly they identified compounds as a potent hypoglycemic agent through percent reduction in blood glucose and adipocyte differentiation; however, these compounds caused cardiac hyper-

trophy after multiple oral administrations and also caused high concentration in blood (i.e., tendency to accumulate over the course of administration). Then, they tried to reduce the drug accumulation by introducing the functional groups that can be metabolized *in vivo* easily, as a resulting compound **30** (1 mg/kg) with methoxy substitution at 5-position of imidazopyridine ring (5-[4-(5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-2-ylmethoxy)benzyl]-TZD) showed relatively high adipocyte differentiation but did not reduce blood glucose level due to poor oral bioavailability. However, compound **30** had shown to reduce blood glucose (55.8%) when it was administered orally as an admixture with food for 1 week. On the other hand, compound **30** has shown to exhibit poor dissolution rate, hence they improved the solubility of compound **30** by converting them into salt form (HCl and fumaric acid). As a result, HCl salt of compound **30** improved hypoglycemic effect with ED₂₅ value of 0.02 mg/kg/day in comparison to that of rosiglitazone maleate (0.39 mg/kg/day). On the basis of above results, TZD-HCl salt of compound **30** was selected as the candidate for further studies (Table 3 and 4) [75].

Madhavan et al. prepared a series of phthalazinones based TZD derivatives by treating phthalazinones (**31**) with 4-(2-bromoethoxy)benzaldehyde in the presence of K₂CO₃ in dimethylformamide (DMF) at 70 °C for 2–6 h to yield phthalazinones substituted aldehyde (**32**) which was further treated with TZD (**3**) in the presence of piperidine benzoate to furnish benzylidene TZD analogs (**33**) and was then reduced using 10% Pd/C catalyst to give 5-(4-[2-(4-methyl-1-oxo-1,2-dihydrophthalazin-2-yl)ethoxy]phenylmethyl)TZD (or 5-benzyl-TZDs) (**34**) as shown in **S8**. The synthesized compounds were screened for both *in vivo* (*db/db* mice) and *in vitro* (PPAR- γ transactivation in the human embryonic kidney (HEK) 293T cells) activity. From the synthesized series, compound **34** was the most potent PPAR- γ activator and also

demonstrated to lower both glucose (72%) and TGs (68%) levels (Table 3 and 4) [76].

Madhavan et al. synthesized a series of pyrimidinone derivatives of TZDs by condensation of pyrimidinone substituted aldehydes (35) with TZDs to give unsaturated compounds (36), which was further reduced to give the final product (37) as shown in S9. Of note, compound 35 was synthesized through a coupling reaction between substituted pyrimidinone and 4-[2-bromoethoxy]benzaldehyde. The synthesized compounds were examined for plasma glucose and TGs lowering activity in *db/db* mouse and the effects were compared to both rosiglitazone and pioglitazone as a standard. In a preliminary study, compounds were evaluated for 6-days at a dose of 30 or 100 mg/kg in *db/db* mice. Among various compounds, 5-(4-(2-(2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl)ethoxy)phenyl methyl)TZD (PMT13) (37) exhibited superior activity (73% reduction in plasma glucose and 85% reduction in TG level) than rosiglitazone (65% reduction in plasma glucose and 41% reduction in TG level). Other synthesized derivatives showed less effect even at a higher dose (100 mg/kg). Subsequently, dose-dependent study (0.3, 3 and 10 mg/kg) was carried out for 15 days in the same genetic models. As a result, PMT13 (37) showed a better reduction in hypoglycemic and hypolipidemic activity than rosiglitazone and pioglitazone. During subacute toxicity studies for 28 days, PMT13 (37) at 100 mg/kg produced neither mortality nor any evidence of toxicity measured through changes in the body weight or food consumption. The synthesized compounds were also evaluated for PPAR- γ transactivation study using HEK 293T cells. PMT13 at lower concentration (0.010 μ M) showed better PPAR- γ activation than rosiglitazone but showed similar activation at higher concentration (5.0 μ M). In contrast, PMT13 (37) was shown to exhibit better activation towards PPAR- γ than pioglitazone (Table 3 and 4) [77].

Storr et al. synthesized a series of vanadium compounds (42) through chelation of ligand having TZD precursor (41) and vanadium sulphate as shown in S10. TZD precursor is prepared from compound (38), which was coupled with 4-hydroxybenzaldehyde (6) to afford the aldehyde (39). Next, Knoevenagel condensation was carried out using aldehyde (39) and TZD to get compound (40), on which deprotection was carried out in acidic condition to afford precursor (41). All the compounds were evaluated for insulin enhancing capability in streptozotocin (STZ)-induced diabetic rats through percent reduction in the blood glucose level and the effects were compared with rosiglitazone and BMOV. The compounds were administered at a dose of 0.1 mmol/kg. Complex 42 showed the most efficient hypoglycemic effects than the ligands without chelation. The hypoglycemic effects were superior and comparable to that of rosiglitazone and BMOV, respectively (Table 4) [78].

Koyama et al. synthesized a series of 5-aryl TZDs containing 4-phenoxyphenyl side chains (47) as shown in S11. Mandelates (43) were treated with 1,3-dibromopropane or 1,4-dibromobutane in DMF to give ether linkage derivative (44), which further underwent coupling reaction with 4-(4-(methylsulfonyl)phenoxy)-2-propylphenol (45) to give 46, then standard TZD protocol was applied to 46 to yield the final derivatives (47) and evaluated them for both *in vivo* (*db/db* mice) and *in vitro* (PPAR- γ) activities. Firstly, they evaluated functional activity (PPAR- γ) and pharmacokinetic profile of synthesized compounds. The PPAR- γ transactivation assay was performed as reported previously using COS-1 cells [79]. Then, compounds with good functional activity and pharmacokinetic profiles were evaluated *in vivo*. The synthesized compounds were administered as sodium salt at a dose of 5 and 10 mg/kg for 11 days. Among the synthesized compounds, compound 47 exhibited good oral bioavailability similar to rosiglitazone. Compound 47 showed a dose-dependent reduction in plasma glucose and TG in *db/db* mice despite its weak PPAR- γ activity than rosiglitazone.

The reduced functional activity may be due to longer half-life ($t_{1/2}$ = 2.8 h) than the reference compound ($t_{1/2}$ = 1.2 h) (Table 3 and 4) [80].

Kim et al. reported a series of substituted pyridines and purines having 2,4-TZDs moiety and synthesized them from their respective pyridines and purines in order to increase the hydrophobic properties as shown in S12. Firstly, 5-amino-2-chloropyridine (48) was converted into 5-substituted pyridines (49) using either simple aromatic hydrocarbon or substituted heteroaromatic compound in the presence of isoamyl nitrite and copper (I) oxide followed by amination with 2-methylaminoethanol yielded amino alcohols (50). Then, the compound 50 treated with 4-fluorobenzaldehyde in the presence of NaH to give aldehyde compounds (51), which underwent Knoevenagel condensation to give unsaturated TZD analogs (52) in turn reduced into desired compound (53) through using Pd(OH)₂. The synthesized compounds were evaluated for their hypoglycemic and hypolipidemic activity (*in vitro* and *in vivo*). The *in vitro* effect was observed for the TGs accumulation in 3T3-L1 cells by keeping the concentration of test compounds in the range of 3×10^{-5} – 3×10^{-11} M. Among the various compounds, compound 53 (5-(4-{2-[N-methyl-(5-phenyl-pyridin-2yl)amino]ethoxy}benzyl)thiazolidine-2,4-dione) increased insulin-induced TG accumulation in 3T3-L1 cells with EC₅₀ value of 0.00054 μ M in comparison to rosiglitazone and pioglitazone. Further, they evaluated the potent compounds *in vivo* based on the *in vitro* results. The *in vivo* activity was performed in KKA^V mice for 5 days. The synthesized compounds were administered at a dose of 1, 6 and 30 mg/kg. The hypoglycemic and hypolipidemic activity were estimated through ED₂₅ value. The compound 53 found to reduce 25% blood glucose and TG (ED₂₅ = 0.020 and 2.5 mg/kg/day, respectively) in comparison to that of rosiglitazone and pioglitazone. These results suggested that TZD compound 53 showed to be more effective than the reference standards and was selected for further pharmacological studies (Table 3 and 4) [81].

Gupta et al. reported a series of substituted 5-(4-(2-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethoxy)benzylidene)TZDs (57) which were synthesized by the coupling of 6,7-dimethyl-1,2,3,4-tetrahydroquinoxalin-3-one (54) and 4-(2-bromoethoxy)benzaldehyde (55) in the presence of NaH in dry DMF to afford 4-(2-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethoxy)benzaldehyde (56) which in turn underwent Knoevenagel condensation with TZD yielded 57 as shown in S13. These synthesized derivatives were screened for euglycemic and hypolipidemic activities in Wistar male rats and were administered at doses of 3, 10, 30 and 100 mg/kg for 14–15 days. OGTT was also carried out on the final day by loading glucose at a dose of 3 g/kg. Among these series, compound 57 showed a dose-dependent reduction in plasma glucose and TG in comparison to those in rosiglitazone (Table 4) [82].

Lee et al. designed novel substituted pyrimidines containing TZD analogs by treating 4,6-dichloropyrimidine (58) and substituted aromatic alcohols in the presence of NaH to give 4-substituted pyrimidines (59), which underwent amination with 2-methylaminoethanol to afford substituted N-methylaminoethanol derivative (60). The compound 60 was further reacted with 4-fluorobenzaldehyde to yield benzaldehyde derivatives (61), which then underwent Knoevenagel condensation to give unsaturated TZD analogs (62) and were reduced further to give the product (63a and b) as depicted in S14. The compounds were tested for their glucose and lipid-lowering activity in KKA^V mice. Test compounds were administered orally at a dose of 1, 6 and 30 mg/kg for 5 days. Among the synthesized analogs, compounds 63a and b have significantly attenuated the hyperglycemic activity when compared to pioglitazone and rosiglitazone. Compounds 63a and b showed comparable potency to

pioglitazone in terms of reducing TG level, whereas rosiglitazone failed to show the hypolipidemic activity. Further, the compounds (3×10^{-5} – 3×10^{-11} M) were evaluated for the accumulation of TG in 3T3-L1 after insulin differentiation. The study results demonstrated that almost all the 4- or 5-substituted pyrimidine derivatives showed better results on TG accumulation in 3T3-L1 cells than that of rosiglitazone and pioglitazone except for the compound substituted with phenylamino at the 4th position of pyrimidine and 2-thiophenyl at the 5th position of pyrimidine. Whereas, 2-substituted pyrimidines showed inferior activity compared to 4 or 5-substituted pyrimidine derivatives (Table 3 and 4) [83].

Gim et al. reported the synthesis of novel TZD derivative, 5-(4-(2-(methyl-*p*-substituted phenylamino)ethoxy)benzyl)TZD (66) by Mitsunobu reaction as shown in S15. The compound 66 was prepared by the reaction between 2-(methyl-*p*-substituted phenylamino) ethanol (64) and *N*-tritylated 5-(4-hydroxybenzyl)TZD (28) using tributylphosphine (Bu_3P) and 1,1'-(azo-dicarbonyl)dipiperidine (ADDP) to afford the compound 65, then treatment of compound 65 with TFA yielded the final derivative 66. The compounds were evaluated for PPAR- γ agonistic activity in CV-1 cells and inhibition of nitric oxide (NO) production in the murine macrophage cell line (RAW 264.7). As a result, except compound 66, all the synthesized compounds found to exhibit very low PPAR- γ activity and NO inhibition. The compound 66 was reported to exhibit potent activity with 21.2% PPAR- γ activation in comparison with PPAR- γ activator (i.e., GW409544) and 51.5% NO inhibition compared to standard (Table 3) [84].

Iqbal et al. designed novel TZD derivatives that are structural analogs of pioglitazone, by introducing pharmacologically important heterocycles specifically, thiazole, triazole and oxadiazole nucleus linked to the middle phenyl ring through heteroatom linkage with one/two carbon atom. The compound of interest was obtained through base-catalyzed nucleophilic substitution reaction of 4-(2-bromoethoxy)benzaldehyde (55) with 2-mercaptotriazoles/2-mercaptooxadiazole (67) at room temperature to yield the intermediate (68). This intermediate was then refluxed with TZD in toluene, with a catalytic amount of piperidine to get the target compounds (69a and 70a and b) (S16). The synthesized compounds were evaluated for their *in vivo* hypoglycemic and hypolipidemic activities against alloxan-induced diabetic male Wistar rats. The compounds were treated orally to the rats for 15 days at different dose levels (3, 10, 30 and 100 mg/kg body weight) and the effects (i.e. percentage reduction of plasma glucose and TG) were compared with pioglitazone. The compounds (69a, 70a and b) showed comparable hypoglycemic and hypolipidemic activity with that of the standard pioglitazone. The compound containing 3-pyridyl substitution at the 5th position of oxadiazole (70a) was shown to be more potent in terms of percent reduction of glucose in comparison to that of pioglitazone in diabetic rats (Table 4) [85].

Kumar et al. reported a series of novel glitazones incorporated with phenols by using S17. 4-(2-bromoethoxy)benzaldehyde (55) was refluxed with various substituted phenols in dry acetone to give various phenol substituted 4-(2-bromoethoxy)benzaldehydes (71) which in turn underwent Knoevenagel condensation with TZD (3) or rhodamine to yield the final derivatives (72a, b and 73a, b). The synthesized derivatives were screened for *in vitro* insulin-induced glucose uptake using rat hemidiaphragm and also the cytotoxicity by sulforhodamine assay using human epithelial type 2 cells (HEp-2) and A549 cells. Compound 73a with TZD ring showed better glucose uptake activity (38.0 mg/dL/45 min) than others and the effect was comparable to that of standard (37.0 mg/dL/45 min). In the cytotoxicity assay, compound 72a with rhodamine ring showed cytotoxicity in both cells (Table 3) [86].

To circumvent TZD side effects like weight gain, hepatotoxicity, and fluid retention, Shukla et al. designed a new series of coumarin-based TZD analogs and its bioisosteres (oxazolidinone and imidazolidinone) (85, 86 and 87) as shown in S18. The resorcinol (74) was condensed with ethylacetoacetate (75) using Pechman reaction to afford 7-hydroxy-4-methyl coumarin (76), which was brominated by NBS to give 7-hydroxy-4-bromomethyl coumarin (77) followed by reaction with 4-hydroxy benzaldehyde to afford 4-(7-hydroxy-2-oxo-2H-chromen-4-yl)methoxy)benzaldehyde (78). This compound upon Knoevenagel condensation with TZD (3), 2,4-oxazolidinone (79) and 2,4-imidazolidinone (80) yielded coumarin-based bioisosteric analogs (81, 82 and 83) followed by refluxing with substituted benzyl chloride (84) afforded the desired products (85a-c, 86a-c, and 87a-c). The synthesized compounds were then evaluated for antidiabetic activity in STZ-induced diabetic rats. Firstly, the dose selection study was carried out using these three bioisosteric analogs (85, 86 and 87) at different dose level (15, 25, 35 and 45 $\mu\text{mol/kg}$) for the duration of 3, 7, 10 and 15 days. As a result, 35 $\mu\text{mol/kg}$ dose was found to be most effective in reducing plasma glucose level and this dose was selected for the subsequent study for the different time periods (i.e., 3, 7, 10 and 15). It was found that compounds having *N*-substituted oxazolidinone moiety (82 and 86a) showed a maximum reduction in plasma glucose level (40.25% and 44.67%, respectively) in comparison to other bioisosteres. Whereas, the standard drug rosiglitazone was more active in lowering plasma glucose levels (56.7%). Molecular docking studies were also carried out against PPAR- γ (PDB ID: 2PRG protein) and the results showed that compounds 82 and 86a showed hydrophilic interaction between the oxygen atom of oxazolidinone and SER342 while hydroxyl group of coumarin moiety showed hydrophobic interaction with HID449 (Table 4) [87].

Ahmedi et al. reported the synthesis of two novel derivatives of rosiglitazone (94 and 98) as shown in S19a and 19b. 2,4-Bis(morpholino)-6-chloro-1,3,5-triazine (90) was synthesized from the reaction of cyanuric chloride (88) and morpholine (89) in DCM. The synthesized compound 90 was then refluxed with 2-methylaminoethanol (91) to afford 2-((4,6-dimorpholino-1,3,5-triazin-2-yl)(methyl)amino)ethanol (92). Then, the final compound 5-(4-(2-((4,6-dimorpholino-1,3,5-triazin-2-yl)(methyl)amino)ethoxy)benzyl)TZD (94) was synthesized by mixing of compounds 92 and 93 in DMSO. On the other hand, compound 5-(2-chloro-4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzyl)TZDs (98) was synthesized by mixing of compound 96 and 97 in DMSO. Compound 96, 2-(*N*-Methyl-*N*-2-(pyridine-2-yl)amino)ethanol was synthesized by heating the mixture of 2-chloropyridine (95) and *N*-methyl ethanolamine (91) at 120 °C. Both the synthesized derivatives (94 and 98) were then screened for antihyperglycemic and antihyperlipidemic activity in the alloxan-induced diabetic rat model for 16 days. The synthesized derivatives and the standard drug rosiglitazone were administered at a dose of 3 mg/kg i.p. and the results were observed for the reduction in blood glucose levels and the lipid profile [TGs, total cholesterol, and low-density lipoprotein (LDL)]. As a result, compound 94 showed a significant reduction in blood glucose (295.5 mg/dL) as compared to control (411.0 mg/dL) and rosiglitazone (304.0 mg/dL). Also, compounds 94 and 98 were able to significantly increase the high-density lipoprotein (HDL) level and HDL/LDL ratio which is considered as a good indicator for the improvement of lipid profile in comparison to rosiglitazone (Table 4) [10].

Deshmukh et al. carried out the Knoevenagel condensation of 2-(4-formyl-phenoxy) substituted quinoline-3-carbonitriles (101) and TZD to design a new series of (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) substituted quinoline-3-carbonitriles (102) as shown in S20. The compound 102 was obtained by reacting substituted 2-chloroquinoline-3-carbaldehyde (99) with

ammonia and molecular iodine in tetrahydrofuran (THF) thereby, yielding substituted 2-chloroquinoline-3-carbonitriles (100) which upon condensation with 4-hydroxy benzaldehyde (6) in DMF gave the compound 101. The synthesized compounds were screened for *in vivo* antidiabetic activity in sucrose (10 g/kg) loaded rat model. Compounds were administered orally at a dose of 100 mg/kg. As a result, compound **102** showed 9.4% improvement on oral glucose tolerance during 0–120 min but the effect was inferior to that of the standard drug i.e., metformin (19.1%) (Table 4) [88].

Structural activity relationship (SAR) studies of alkoxy benzyl analogs

The inclusion of thioethoxy linkage connected to triazole and oxadiazole leads to more potent results. Incorporation of oxazole ring with the substitution of phenyl at the 2nd position is best for hydrophobic interaction with the active site and had a superior activity level. Substitution of X₁ with CH(OH) on the ethoxy chain, showed higher or comparable activity than the substitution with CH₂ but substitution with an oxo group (C=O) decreases the antidiabetic activity. Incorporation of heterocyclic with an indole ring with no substitution exhibited more potent euglycemic and hypolipidemic activities. Incorporation of heterocyclic with tryptophan and carbazole ring completely abolished the activity. Substitution at the 2nd position of pyrimidinone with alkyl group reduced plasma glucose level whereas; increase in the alkyl chain reduced the antidiabetic activity. Replacement of oxygen at the 4-position of a 5-benzyl moiety with sulfur led to completely inactive for hypoglycemic effects. Substitution with electron-withdrawing groups at X position does not have much impact on the activity. The distance between the benzene ring and heterocyclic moiety should be of two carbon atoms. The unsaturated compounds showed lesser results than saturated compounds [71,72,74,76,78,82,86] (Fig. 5A).

Pyrazole based TZDs

Naim et al. carried out the synthesis and molecular docking studies (against PPAR- γ) (PDB ID: 1ZEO) of TZD based benzene sulphonamide derivatives containing pyrazole moiety as shown in S21. Firstly, compound, 4-hydrazinyl-benzenesulphonamide (104) has been synthesized from sulphanilamide (103) through diazotization followed by reduction with SnCl₂. The imines were prepared by refluxing hydrazine (104) with substituted aryl ketones to yield corresponding substituted hydrazones (105). The

compound 105 upon Vilsmeier-Haack reaction with DMF and POCl₃ gave pyrazolecarbaldehydes having *N,N*-dimethyl formimide group (106) which on treatment with sodium hydroxide gave pyrazolecarbaldehydes having benzenesulphonamide group (107) followed by Knoevenagel condensation with TZD to yield the final product (**108a-c**). The compounds having glide scores > 10 were further evaluated *in vitro* for PPAR- γ transactivation assay in HEK-293 cells. Among the eight compounds, compounds 108a-c significantly increased PPAR- γ transactivation (57.3%, 60.5%, and 61.2%, respectively) and the effect was comparable with that of pioglitazone (68.3%) and less than that of rosiglitazone (83.6%). After that, compounds showed good PPAR- γ transactivation were further screened for *in vivo* antidiabetic activity in STZ-induced diabetic rats for 15 days by administering the compounds at a dose of 36 mg/kg. All the three compounds (**108a-c**) showed superior activity in terms of reduction in blood glucose level (138.7, 137.4 and 134.1 mg/dL respectively) than that of standard drug rosiglitazone (143.1 mg/dL) but exhibited comparable potency with that of pioglitazone (132.2 mg/dL). Further, compound (**108c**), which showed the more potent antihyperglycemic effect was evaluated for body weight gain for 1 and 15 days and as a resulting compound **108c** did not show any significant change in body weight. Then, the compounds **108a-c** were analyzed for liver toxicity through assessing the levels of biochemical parameters [aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP)] and histological staining. As a result, compound **108c** showed significant and maximal lowering of these biochemical parameters as compared to pioglitazone while compounds **108a** and **108b** were equipotent to pioglitazone. In the histopathological study, compound **108c** showed no signs of toxicity whereas compound **108a**, **108b** and pioglitazone showed the least pathological changes. From the above results, the compound **108c** was considered as the most potent compound and was further evaluated for PPAR- γ gene expression in 3T3-L1 cells. The results showed that compound **108c** significantly increased PPAR- γ gene expression by 1.9 folds whereas expression was increased 1.2 and 1.5 folds for the standard drugs rosiglitazone and pioglitazone, respectively (Table 3 and 4) [89].

Naim et al. synthesized a series of TZDs coupled with pyrazole as shown in S22. The compounds 110 were synthesized by refluxing aryl ketones with phenylhydrazine (109), which further underwent Vilsmeier-Haack reaction to afford pyrazole carbaldehydes (111) which in turn further reacted with TZD to furnish the final product (**112a-c**). Firstly, molecular docking studies were carried

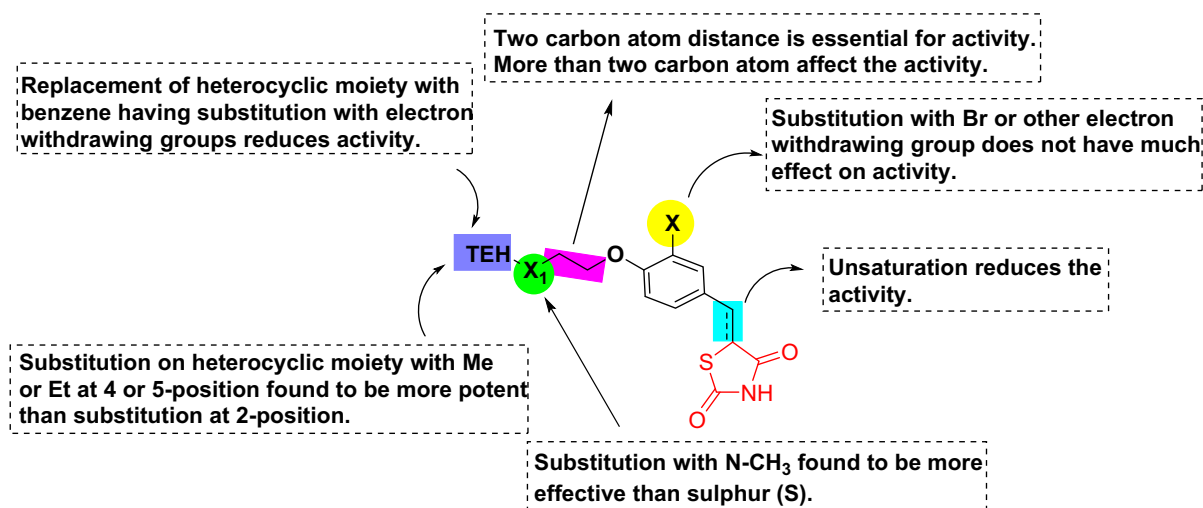


Fig. 5A. SAR of ethoxy benzyl based TZD analogs (structures are original and made by using chem draw ultra 12.0).

out against PPAR- γ (PDB ID: 2PRG) and the compounds with glide scores > -8 were selected further for PPAR- γ transactivation assay (HEK-293 cells) and *in vivo* antidiabetic activity in STZ-induced diabetic rats. As a result, compounds **112a-c** showed significant PPAR- γ transactivation (48.65, 51.30 and 52.06%, respectively) and the results were comparable to those of standard drugs (pioglitazone (65.22%) and rosiglitazone (85.30%)). The *in vivo* study carried out on the synthesized compounds for 15 days at a dose of 36 mg/kg also produced similar results with that of *in vitro*. Compounds (**112a-c**) displayed significant reduction in blood glucose levels (150.7, 141.4 and 140.1 mg/dL), which were comparable to those of standard drugs pioglitazone (135.2 mg/dL) and rosiglitazone (141.1 mg/dL). Further, compound **112c** was evaluated on body weight gain for 15 days, as a result, compound **112c** did not show any significant change in body weight, which suggests that the weight neutral effect exhibited by the compound **112c**. Then, the hepatotoxicity study was carried out with the compounds (**112a-c**) at 3 times higher dose (i.e., 108 mg/kg) that was used in the antidiabetic activity (36 mg/kg). As a result, compound **112c** came out to be most potent in terms of lowering the levels of AST, ALT and ALP and did not cause any toxic effect to the liver but the compound **112a** showed a small dilation of sinusoidal space along with pioglitazone. After that compound **112c** was evaluated for PPAR- γ gene expression in 3T3-L1 cells and the results showed that compound **112c** significantly increased the PPAR- γ gene expression (2.35 fold) in comparison to that of pioglitazone (1.6 fold) and rosiglitazone (1.27 fold) and also increased the levels of GLUT1 and GLUT4 [90]. Altogether, study results demonstrated that compound with naphthalene moiety (**112c**) showed a more potent antihyperglycemic activity with devoid of any side effect that was observed with the standard drugs (Table 3 and 4) [91].

We have recently synthesized TZDs clubbed with pyrazoles analogues. The title compounds were synthesized using a synthetic procedure involving 4-steps and the synthetic strategy is outlined in Scheme S23. The first step involves the same procedure for the synthesis of TZD (3) as highlighted in Scheme S1. After that, substituted pyrazole carbaldehydes (111) were made through Vilsmeier-Haack reaction on substituted hydrazones (110), which in turn were synthesized by treating substituted acetophenones with phenylhydrazine (109) as shown in Scheme S22. Next, *N*-alkylation and acidification of TZD (3) was carried out with benzyl bromide (113) and bromoacetic acid (114), respectively to yield *N*-alkylated (115a) and acidified TZD (115b) followed by Knoevenagel condensation with synthesized carbaldehydes to yield TZD clubbed pyrazole adducts (**116a and b**). The compounds were docked

against PPAR- γ (PDB ID: 2PRG) and alpha-amylase (PDB ID: 4GQR) and further evaluated for *in vivo* and *in vitro* antidiabetic activity, in addition to *in vitro* anti-inflammatory and antioxidant activities. Compound **116b** exhibited significant blood glucose-lowering activity (134.46 mg/dL) and was found to be similar to standard pioglitazone (136.56 mg/dL). In addition, the compound (**116b**, IC₅₀ 4.08 μ g/mL) was also found to be a potent inhibitor of alpha-amylase. These results were consistent with *in vitro* docking results with PPAR- γ and amylase. Compound **116a** was found to exhibit anti-inflammatory and antioxidant activity to a greater extent through reducing inflammatory markers (TNF- α , and IL- β) and oxidative stress marker (MDA). These results suggest that compounds (**116a and b**) can be considered as a promising candidates for the discovery of new antidiabetics [92].

SAR of pyrazole based TZD analogs

Substitution with bulkier aryl groups at the *N*-position of pyrazole ring showed strong hydrophobic interactions with receptor site. Substitution with smaller halogens (X and X₁) at *meta* and *para* positions of the phenyl ring of the 3rd position of pyrazole significantly reduced blood glucose levels but electron releasing groups lowers the antidiabetic activity. Replacement of aromatic ring (green colored) with thiophene reduces the activity but with large hydrophobic naphthalene moiety increases the antidiabetic activity. The acidic head derivatives resulted in more potent activity in comparison to benzylated TZD [89–92] (Fig. 5B).

N-substituted TZDs

Datar et al. synthesized 5-substituted benzylidene TZD-3-acetic acid derivatives based on 2D-QSAR studies as shown in S24. Firstly, benzylidene derivatives (117) upon *N*-alkylation with ethyl bromoacetate gave 5-substituted benzylidene-2,4-dioxothiazolidin-3-yl-acetic acid ethyl ester (118) followed by acidic hydrolysis with conc. HCl gave the final compound as acid derivatives (**119a and b**). The synthesized derivatives were then evaluated for their hypoglycemic effect using a sucrose loaded model. The compounds were administered orally at a dose of 100 mg/kg and the effects were observed as a percentage reduction in blood glucose level. The results showed that the analogs with di- and trimethoxy group (**119a and b**) on phenyl ring showed reduction in blood glucose level within 30 min and the effect was maintained till the duration of 120 min, whereas pioglitazone showed a decrease in blood

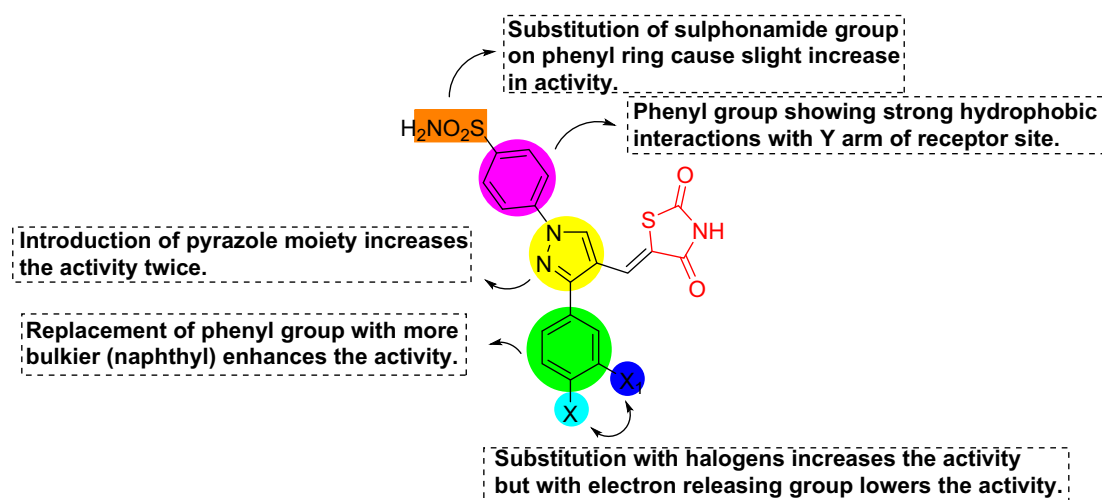


Fig. 5B. SAR of pyrazole based TZD analogs (structures are original and made by using chem draw ultra 12.0).

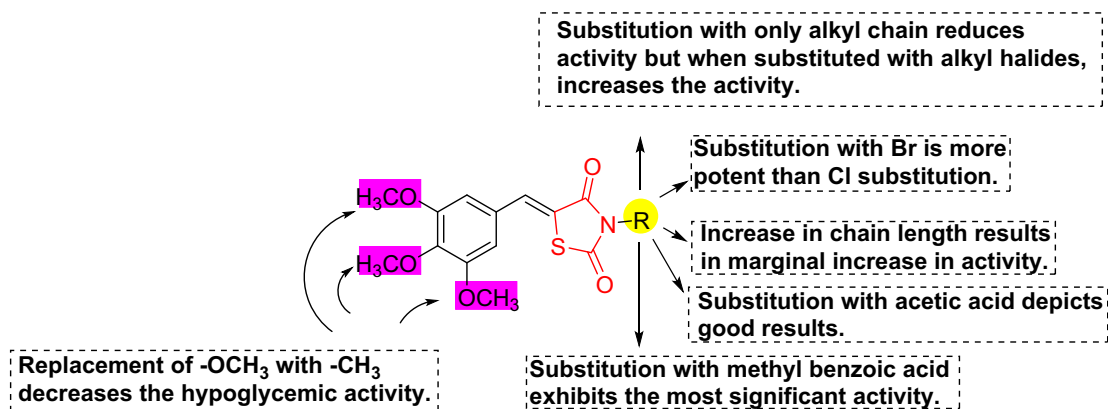


Fig. 6A. SAR of N-substituted TZD analogs (structures are original and made by using chem draw ultra 12.0).

glucose level in 30 min and later slightly increased levels of blood glucose in 60, 90 and 120 min (Table 4) [93].

SAR of N-substituted TZD analogs

Substitution with dimethoxy or trimethoxy at the benzene ring showed similar hypoglycemic activity as compared to pioglitazone but when replaced with the hydroxyl group lowers the activity. By maintaining the acidic nature of the TZD head, results in more potent activity [93] (Fig. 6A).

Flavonyl based TZDs

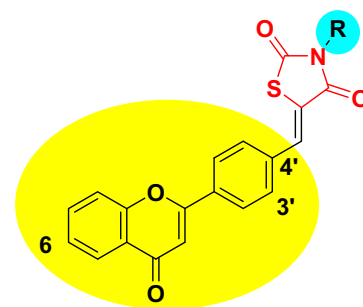
Tunçbilek et al. synthesized a new series of 3-substituted benzyl-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-TZD derivatives as shown in **S25** by carrying out Knoevenagel condensation of N-substituted derivative (120) with flavone-6-carboxaldehyde (121) and flavone-4'-carboxaldehyde (4-(4-oxo-4H-chromen-2-yl)benzaldehyde) (122) to yield 3-(p-substituted benzyl)-5-(6- and 4'-flavonyl) TZD derivatives (**123a** and **b** and **124a-c**, respectively). The compounds were then evaluated for insulinotropic activity *in vitro* using insulin-secreting cells (INS-1) cells. The effects were observed at different concentrations (1 and 10 µg/mL) in comparison to the reference standard glibenclamide (1 µg/mL). It was found that compounds **123a** and **b** and **124a-c** were able to increase the insulin release (105–140%) more than the other derivatives at higher concentration (10 µg/mL) whereas the glibenclamide was able to increase the insulin release (210.4%) at 1 µg/mL (Table 3) [94].

Bozdog-Dundar et al. designed a new series of flavonyl-2,4-TZDs by carrying out Knoevenagel condensation of flavone-aldehyde (125) with ethyl 2,4-dioxothiazolidine-3-ylacetate (126) thereby, furnishing flavonyl-2,4-TZD acetic acid ethyl ester derivatives (127) followed by acid hydrolysis to yield carboxylic acid derivatives (**128**) (**S26**). The synthesized compounds were screened for insulinotropic activities in INS-1 cells by comparing them with glibenclamide at two different concentrations (0.01 and 0.001 mg/mL). As a result, compound **128** showed the most potent insulin-releasing ability (128.6%) at higher concentration (0.01 mg/mL) in comparison to other synthesized derivatives whereas glibenclamide even at lower concentration (0.001 mg/mL) showed more potent insulin-releasing ability (179.6%) (Table 3) [95].

SAR of flavonyl based TZD analogs

Flavonyl substituted TZDs at 4' position will result in better activity than substituted at 3' or 6 positions. The substitution of

Substitution with acidic group results in more potent activity than the aryl halides.



Position of flavone will be more suitable at 4' rather than 3' or 6 position.

Fig. 6B. SAR of flavonyl based TZD analogs (structures are original and made by using chem draw ultra 12.0).

N with the acetic acid group showed better hypoglycemic activity than the aryl halides [94,95] (Fig. 6B).

Sulfonyl based TZDs

Wrobel et al. prepared the novel 5-(3-aryl-2-propynyl)-5-(arylsulfonyl)TZDs (**133**) and 5-(3-aryl-2-propynyl)-5-(arylsulfonyl)TZDs (**136**) as shown in **S27**. Precursor (arylsulfonyl)TZDs (**131**) were firstly synthesized from aryl thiols (129) and 5-bromoTZDs (130) and the resulted arylsulfonyl TZD upon reaction with 3-arylprop-2-ynyl-bromides (132) and sodium hydride furnished the target compound (133). The compound 129 also converted to arylsulfinic acid upon oxidation with hydrogen peroxide followed by treatment with the base to yield arylsulfinate which in turn underwent treatment with 5-bromoTZDs (130) yielded another precursor (arylsulfonyl)TZDs (134). The resulted arylsulfonyl TZDs upon reaction with 3-arylprop-2-ynyl-bromides (132) and sodium hydride furnished the target compound (**136**). Compound 136 can also be synthesized from 134 by firstly protecting the nitrogen with trityl chloride to give trityl derivative (135) followed by treatment with 3-arylprop-2-ynyl-bromides (132) and deprotection to give the final compound **136**. Firstly, the synthesized derivatives (**133** and **136**) were evaluated for oral antihyperglycemic effect in *db/db* mice model for 4 days by administering the compounds at a dose of 20 and 100 mg/kg. The results showed that sulfonyl TZDs (**136**) were found to be more potent than the sulfonyl

derivatives (**133**) and most of the sulfanyl derivatives (**133**) did not show any significant reduction in plasma glucose levels even at a dose of 100 mg/kg. In arylsulfanyl derivatives (**136**), the compounds substituted with 4-halogens exhibited more potent results at 100 mg/kg and were further evaluated in *ob/ob* mice model for 4 days at a dose of 50 or 100 mg/kg. It was found that compound **136** (65%) surpassed the reference standards, ciglitazone (39%) and BM13.907 (54%) in terms of percentage reduction in insulin. On the other hand, ciglitazone and compound **136** showed equipotent results in terms of percentage reduction in glucose. Then the compound **136** was further screened for glucose tolerance test by subcutaneous administration in *fa/fa* rats for 4 days at a dose of 20 and 100 mg/kg and the reference standard (ciglitazone) at 100 mg/kg. It was found that compound **136** considerably improved glucose tolerance at 20 mg/kg and did not exhibit any effect at 100 mg/kg. The overall results showed that arylsulfanyl TZD derivatives (**136**) were more potent as compared to arylsulfanyl TZD derivatives (129) (Table 4) [96].

Pattan et al. designed a series of TZD derivatives through microwave-assisted reaction of 5-(4-chlorosulfonyl benzylidene)-TZD (**138**) with the various aromatic/heteroaromatic amines (**139**) to give the final product (**140a–f**) as shown in S28. Of note, compound **138** was synthesized by refluxing benzylidene-TZD (**137**) with chlorosulphonic acid. All the synthesized compounds were then evaluated for antidiabetic activity in alloxan-induced diabetic albino rats by administering the test compounds at a dose of 36 mg/kg. Among all the synthesized compounds, compounds **140a–f** produced a significant lowering of blood glucose levels in diabetic rats when compared with standard drug glibenclamide (Table 4) [4].

Jawale et al. designed various TZD derivatives with aryl sulfonyleurea nucleus as shown in S29. The condensation reaction of maleic anhydride (**141**) with thiourea (**1**) yielded 2-imino-4-oxo-5-thiazolidine acetic acid (**142**) which upon hydrolysis gave 2,4-TZD acetic acid (**143**) followed by reaction with thionyl chloride and sodium azide afforded acylazide (**144**) which underwent Curtius rearrangement to yield 5-(isocyanatomethyl)TZD (**145**) which upon condensation with aryl sulfonamides (**146**) furnished the final compound 1-((2,4-dioxothiazolidin-5-yl)methyl)-3-benzene sulfonyleureas (**147a–d**). The newly synthesized derivatives were then screened for antihyperglycemic activity in the sucrose loaded rat model. The synthesized compounds and the reference drug (metformin) were given at a dose of 100 mg/kg. As a result, only four compounds (**147a–d**) repressed the postprandial increase in blood glucose level showing 15.8, 17.2, 14.3 and 16.5% activity, respectively in comparison to that of standard i.e., metformin (27.0%) (Table 4) [97].

SAR of sulfonyl based TZDs

Introduction with sulfonyl group showed good antihyperglycemic activity than the sulfanyl group. Substitution of R with heterocyclic moieties or aryl halides showed better antidiabetic activity than the simple alkyl groups [4,96,97] (Fig. 6C).

Naphthyl based TZD

Prabhakar et al. synthesized novel TZD derivatives by combining two active pharmacophores, namely a TZD nucleus and a methoxy naphthyl moiety of nabumetone (**148**), an anti-inflammatory drug. Knoevenagel condensation of nabumetone (**148**) with TZD (**3**) yields an unsaturated mixture of E & Z (**149**) which upon hydrogenation with Pd/C gives a mixture of diastereoisomers (**150**). Further, they synthesized modified analogs of nabumetone based TZDs by reacting the enol-ketone (**151/152**) with TZD gives Z (**153**) and E (**154**) compounds. Similar reactions of TZD (**3**) with acetyl naroline (**155**), 4-(6-hydroxy-2-naphthyl)-butan-2-one (**156**), 2-acetyl thiophene (**157**) and 2-acetyl furan (**158**) gave their corresponding unsaturated compounds (**159–162**) (S30a–c). The synthesized compounds were then evaluated for antidiabetic activity in *db/db* mice for 6 days and compared against a phase-II antidiabetic candidate, 6-(2-fluorobenzoyloxy)-2-naphthyl derivative of TZD (MCC-555) and troglitazone. The derivatives were administered at a dose of 30 mg/kg. The results showed that unsaturated compound (**149**) exhibited a better reduction in plasma glucose (16%) and TG (50%) level in comparison to saturated compound (**150**) (8% and 44% respectively). The Z-isomer (**153**) also showed a better reduction in plasma glucose (16%) as compared to E-isomer (**154**) which did not show any effect. Also, the compounds **159**, **160** and **162** exhibited good antidiabetic activity as they showed 26, 20 and 16% plasma glucose reduction, respectively but did not show any reduction in TG levels (Table 4) [98].

SAR of naphthyl based TZD analogs

The introduction of naphthalene moiety showed better antidiabetic activity along with some marginal anti-inflammatory activity. Unsaturated compounds showed better antidiabetic activity than the saturated one. For better antidiabetic activity, Z-isomer is preferred as compared to E-isomer. Replacement of naphthalene with thiophene moiety completely abolished the activity [98] (Fig. 7A).

Phenothiazine based TZDs

Saini et al. synthesized phenothiazine based TZD as antidiabetic analogs as shown in S31. Firstly, 10H-phenothiazine (**164**) has been synthesized from diphenylamine (**163**) using sulphur and a catalytic amount of iodine followed by stirring with acetyl chloride gives N-acetyl phenothiazine (**165**) which upon Vilsmeier-Haack reaction yielded N-acetyl phenothiazinal (**166**). The compound **166** on reaction with substituted aniline (**167**) gives corresponding imines (**168**) followed by reaction with TZD and thioglycolic acid to give the final product 4-(10-acetyl-10H-phenothiazin-3-yl)-3-phenylTZD (**169a and b**). The synthesized compounds were then evaluated for antidiabetic activity in STZ-induced diabetic rat model. The compound **169a** was administered for a period of 21 days at a dose of 5 mg/kg and compound **169b** at a dose of 10 mg/kg and was compared to that of rosiglitazone (8 mg/kg). It was found that both the compounds (**169a and b**) exhibited equipotent antidiabetic activity to that of standard therapy (Table 4) [99].

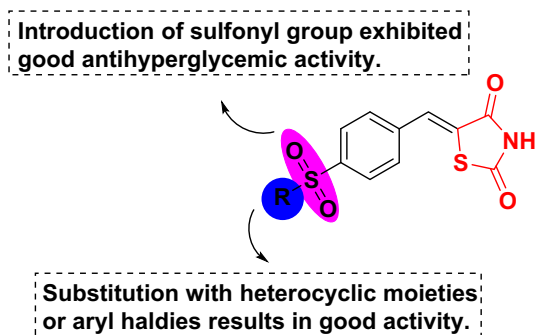


Fig. 6C. SAR of sulfonyl based TZD analogs (structures are original and made by using chem draw ultra 12.0).

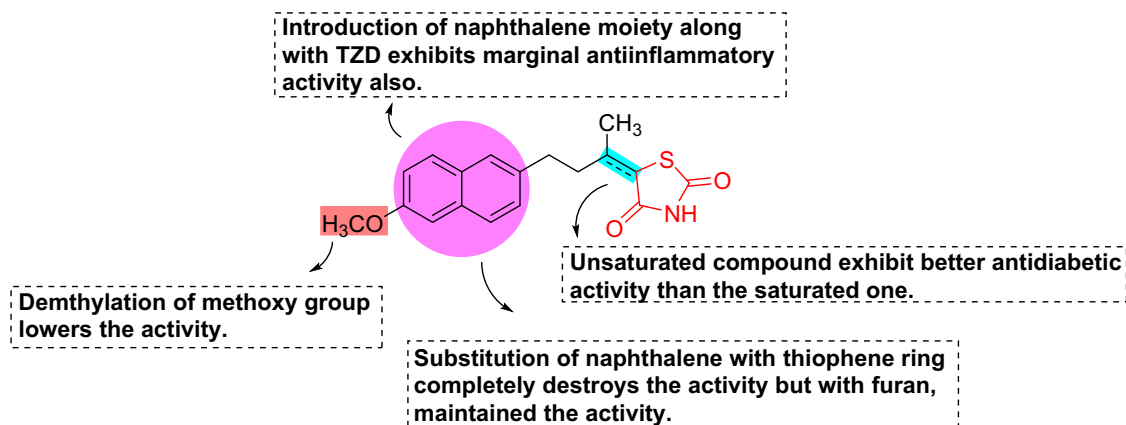


Fig. 7A. SAR of naphthyl based TZD analogs (structures are original and made by using chem draw ultra 12.0).

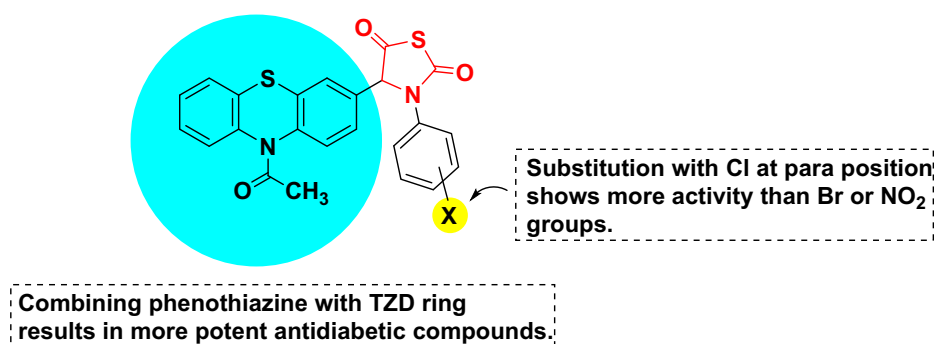


Fig. 7B. SAR of phenothiazine based TZD analogs (structures are original and made by using chem draw ultra 12.0).

SAR of phenothiazine based TZD analogs

By combining phenothiazine moiety with TZD results in good antidiabetic activity. Substitution with chloro group at the *para* position of phenyl rings showed better antidiabetic activity than with bromo or nitro groups [99] (Fig. 7B).

Amide based TZDs

Chittiboyina et al. discovered potent antidiabetic compounds including a series of [1,2]-dithiolanepentamide TZDs as shown in **S32**. Firstly, 4-hydroxybenzaldehyde (6) was coupled with Boc-protected alcohol (170) under Mitsunobu conditions to give *O*-substituted aldehyde (171) followed by condensation with TZD yielded benzylidene derivative (172) which was further reduced with Mg/MeOH to give compound 173. After that, deprotection of Boc was carried out using HCl in dioxane to give the amine hydrochloride compound (174) which was then condensed with dithiolane-substituted acid (175) to give the amide, *N*-(2-(4-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)ethyl)-2-(1,2-dithiolan-3-yl)-*N*-methylpentanamide (**176**) followed by reduction of dithiolane ring to give dithiane compound (177). Compound 177 on further reaction with Boc-glycine (178) gives bis-Boc-glycinates (179) which upon exposure to anhydrous HCl gives another amide derivative, 2,2'-((8-((2-(4-((2,4-dioxo-1,3-thiazolidin-5-yl)methyl)phenoxy)ethyl)(methyl)amino)-8-oxooctane-1,3-diyl)bis(thio))bis(2-oxoethanaminium) dichloride (**180**). The synthesized derivatives (**176** and **180**) were then evaluated for adipocyte differentiation and adipogenesis using 3T3-L1 cells. It was found that compounds **176**, **180** and rosiglitazone equally promoted the differentiation of 3T3-L1 cells, which indicate potent PPAR- γ agonistic

activity. Further, the compound **176** (100 mg/kg) was evaluated for its antidiabetic and hypolipidemic activity in *fal/fa* rat for 1 month. The results showed that there was no change in blood glucose level but there was 78% and 83% reduction in serum insulin and TGs level, respectively while rosiglitazone caused only 40% reduction in TG levels. These results suggest that compound **176** has the potential to treat not only T2DM but also hyperlipidemic state associated with atherosclerosis (Table 3 and 4) [100].

Kumar and Nanjan designed various novel glitazones as PPAR- γ agonists and synthesized them as shown in **S33**. Firstly, acylated amines (181) were reacted with vanillin to give compound 182 which upon condensation with TZD gives the final compound (**183**). Compound 182 on further reduction with Pd over charcoal gave the saturated product (**184**). The synthesized compounds were evaluated for their *in vitro* antihyperglycemic activity by measuring glucose uptake using rat hemidiaphragm model, in the presence and absence of insulin. Although some of the synthesized derivatives showed good glucose uptake activity but the compound, 2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-2-methoxyphenoxy)-*N*-(4-methoxyphenyl)acetamide (**183**) exhibited the highest glucose uptake activity (36.25 mg/g/45 min) as compared to rosiglitazone (35.25 mg/g/45 min) (Table 3) [101].

Kumar et al. synthesized a series of novel glitazones by adding glycine, aromatic and alicyclic amine through two carbon linkers using both conventional and microwave methods as shown in schemes **S34a–c**. In **S34a**, firstly, the C-terminal of glycine (185) was converted to ethyl ester (186) followed by *N*-acylation with chloroacetyl chloride to give 187. Side by, compound 188 was further converted to potassium salt (189) with the help of KOH. Then, compound 189 was coupled with 187 in the presence of DMF to get the final compound, (Z)-ethyl-2-(2-(5(4-methoxybenzy

lidene)-2,4-dioxothiazolidin-3-yl)acetamido)acetate (**190**). In **S34b**, firstly, aromatic/alicyclic amines (191) was treated with the chloroacetyl chloride to get acylated amines (192), which were then reacted with *p*-hydroxybenzaldehyde (6) to obtain compound 193 which upon condensation with TZD yield the final product, (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-*N*-phenylacetamide (**194**). In **S34c**, firstly, aniline (196) was acylated to form 2-chloro-*N*-phenylacetamide (197) which was then coupled with potassium salt of TZD (195) to form 2-(2,4-dioxothiazolidin-3-yl)-*N*-phenylacetamide (198) followed by Knoevenagel condensation with aryl aldehydes to get the final product (**199a–e**). The synthesized compounds were tested *in vitro* at two different dose levels (1 and 2 mg) for glucose uptake activity using rat hemidiaphragm model. As a result, compounds **190**, **194** and **199a–e** depicted significant glucose uptake activity but the compound **199a** was the most potent among all the glitazones having 42.16 mg/dL/45 min of glucose uptake level and the effect was comparable to that of standard drug rosiglitazone (48.34 mg/dL/45 min). The results also showed that increasing the concentration of drugs from 1 mg to 2 mg, did not produce a significant change in glucose uptake level (**Table 3**) [102].

Munj and Ghosh reported the synthesis of two novel benzylidene TZD derivatives namely (Z)-5-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-acetyl)-2-hydroxybenzamide (**202**) and (Z)-5-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-*N*-(5-nitro-thiazol-2-yl)acetamide (**205**) as shown in **S35a** and **S35b**. In **S35a**, the final derivative (**202**) was synthesized by the condensation of compound 200 and 5-(2-bromoacetyl)-2-hydroxy benzamide (201) in the presence of basic condition (K_2CO_3 in DMF). In **S35b**, intermediate 204 was synthesized by the base-catalyzed bromoacetylation of 5-nitro-2-aminothiazole (203) with bromoacetyl bromide which was then condensed with compound 200 to get the final product (**205**). The newly synthesized derivatives were screened for hypoglycemic and hypolipidemic activity against high-fat diet (HFD) and STZ-induced T2DM in Sprague-Dawley rats. The synthesized compounds were administered at a dose of 20 mg/kg and pioglitazone hydrochloride at a dose of 10 mg/kg for 14 days. The results showed that compounds **202** and **205** exhibited significant antihyperglycemic (64% and 56% reduction in the blood glucose) and hypolipidemic activity (74% and 78% reduction in TG and 89% and 92% reduction in cholesterol levels, respectively) and the effect was comparable to that of standard drug (**Table 4**) [103].

Shrivastava et al. reported the synthesis of a few methylphenylbenzamide derivatives having an amide linkage between the central aryl ring and the hydrophobic tail as shown in **S36**. Firstly, compound 5-(4-nitrobenzylidene)TZD (206) was reduced to obtain the amino intermediate 207 which was further reacted with various substituted benzoyl chlorides (208) to furnish the final amide compounds (2,4-dioxo-1,3-thiazolidine-5-yl)methylphenylbenzamide (**209a** and **b**). After that, synthesized derivatives were screened for acute oral toxicity test at a dose of 100 mg/kg in healthy albino rats for 14 days. As a result, compounds did not show any signs of mortality even at a dose of 500 mg/kg after 14 days of administration. Further, compounds were evaluated in STZ-nicotinamide (NA)-induced diabetic rats by administering at a dose of 1, 10 and 100 mg/kg. The results showed that compounds (**209a** and **b**) significantly decreased plasma glucose and TG levels in a dose-dependent manner after the 1-week duration of treatment in comparison to diabetic control and showed comparable potency to that of pioglitazone. However, chloro-substituted derivative (**209a**) at 10 and 100 mg/kg exhibited more potent activity than that of standard therapy at the same dose. Molecular docking studies were also carried out against PPAR- γ and it was found that both the compounds (**209a** and **b**) showed noteworthy

binding energies (–6.1 and –6.3, respectively), close to that of pioglitazone (–7.75) (**Table 4**) [104].

Dadasaheb et al. carried out the reaction between 5-(4-hydroxybenzylidene)-TZD (200)/5-(4-hydroxy-3-methoxybenzylidene)-TZD (210) and aromatic 2-chloro-*N*-substituted acetamide (211) at room temperature to synthesize their corresponding TZD derivatives (**212a** and **b** and **213a** and **b**, respectively) as shown in **S37**. Of note, compounds 200 and 210 were synthesized by the Knoevenagel condensation of TZD with their respective benzaldehydes. The synthesized compounds were then screened for antidiabetic activity at a dose of 30 mg/kg in dexamethasone (1 mg/kg)-induced diabetic-mice for 7 days and were compared against pioglitazone (30 mg/kg) and metformin (30 mg/kg). The plasma glucose levels were assessed at a different time interval after 7 days of treatment. It was found that compound **212a** and **b** and **213a** and **b** significantly decreased the blood glucose level (113.7 mg/dL and 129.9 mg/dL) in comparison to diabetic control (330.1 mg/dL). The compound **212a** and **b** were more potent in comparison to the standard drugs (pioglitazone, 120.2 mg/dL, and metformin, 122.7 mg/dL) in terms of reducing plasma glucose level whereas compound **213a** and **b** showed comparable potency to that of standard. Molecular docking studies were also carried out against PPAR- γ (PDB ID: 2PRG) and the most active compound was found to be **212a** because of its increased contact with receptor active site due to the introduction of an extra hydrophobic group (**Table 4**) [105].

Naim et al. synthesized a series of TZD based amide derivatives (**214**) by reacting the compound 112 with 2-chloroacetamide as shown in **S38**. The compound 112 was synthesized as shown in **S22**. Firstly, molecular docking studies were carried out against PPAR- γ (PDB ID: 3TY0) and as a result, compounds having glide score in the range of –9.0 to 10.5 were further screened for *in vivo* antidiabetic activity in STZ-induced diabetic rats. The compounds were administered at a dose of 36 mg/kg for 15 days and the effects were observed for their reduction in blood glucose level in comparison to standard drugs (pioglitazone and rosiglitazone). It was found that compound **214** showed a significant reduction in blood glucose level (142.4 mg/dL) in comparison to that of diabetic control (325 mg/dL) and the effect was comparable to that of pioglitazone (134.8 mg/dL) and rosiglitazone (144.6 mg/dL). The selected compounds were then further evaluated for PPAR- γ transactivation assay using HEK-293 cells. Compound **214** significantly increased PPAR- γ transactivation (53.65%) in comparison to that of control but the effect was not as much of pioglitazone (62.21%) and rosiglitazone (86.4%). Further, compound **214** was screened for PPAR- γ gene expression studies using 3T3-L1 cells. As a result, compound **214** exhibited a 2.1 folds increase in PPAR- γ gene expression in comparison to that of pioglitazone (1.15 folds) and rosiglitazone (1.64-fold). In addition, the toxicity study was carried out with compound **214** through assessing body weight gain and biochemical parameters and morphological changes in the liver. As a result, compound **214** did not show any signs of toxicity (no change in weight gain and decreased the levels of AST, ALT, and ALP), whereas pioglitazone exhibited mild dilation and inflammation in the sinusoidal space of central vein and in the portal triad, respectively. From all the studies, it was revealed that compound **214** exhibited a potent antidiabetic activity both in terms of *in vivo* and *in vitro* studies (**Table 3** and **4**) [106].

SAR of amide based TZD analogs

The introduction of an extra hydrophobic group increases the binding efficacy with the receptor site. The chain length of two carbon atoms between the terminal nitrogen of amide and the oxygen next to the benzene ring is significant for antidiabetic activity. Substitution with electron releasing groups on the benzene ring does

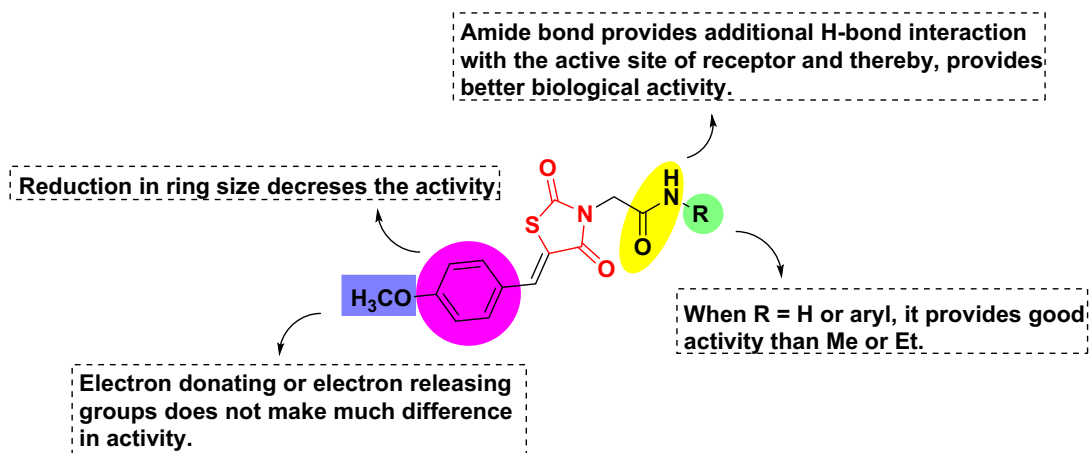


Fig. 8A. SAR of amide-based analogs substituted at N-position of TZD (structures are original and made by using chem draw ultra 12.0).

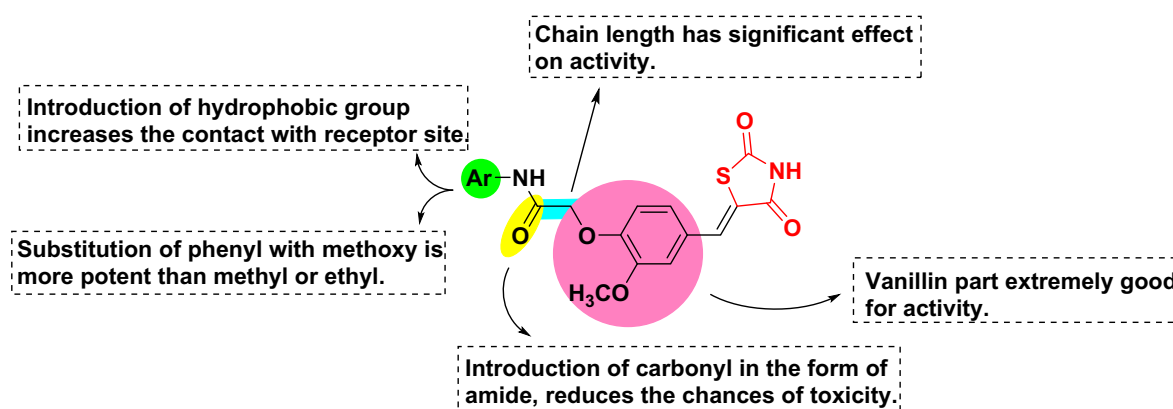


Fig. 8B. SAR of amide-based analogs substituted at 5th position of TZD (structures are original and made by using chem draw ultra 12.0).

not have much effect on activity. The polar TZDs as their head group showed good activity than its bioisosteres (2-thioxo-thiazolidine-4-ones or rhodanine). The activity got reduced on decreasing the ring size from benzene to furan [100–102,106] (Figs. 8A and 8B).

Imidazo-thiadiazole based TZDs

Khazi et al. synthesized a series of eighteen 5-(2-alkyl/aryl-6-aryl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene-1,3-TZDs as

shown in **S39**. The condensation of substituted 2-aminothiadiazole (215) with α -haloaryl ketones (216) under reflux furnished a fused imidazo[2,1-b][1,3,4]thiadiazole nucleus (217) which upon Vilsmeier-Haack reaction gives carbaldehyde (218) followed by Knoevenagel condensation with TZD to give the final product (219a–c). All the synthesized derivatives were then evaluated for *in vivo* hypoglycaemic and hypolipidemic activity in alloxan-induced male Wistar rats by administering at a dose of 3, 10, 30 and 100 mg/kg, and the results were compared against pioglitazone. After the study period of 15 days, it was found that

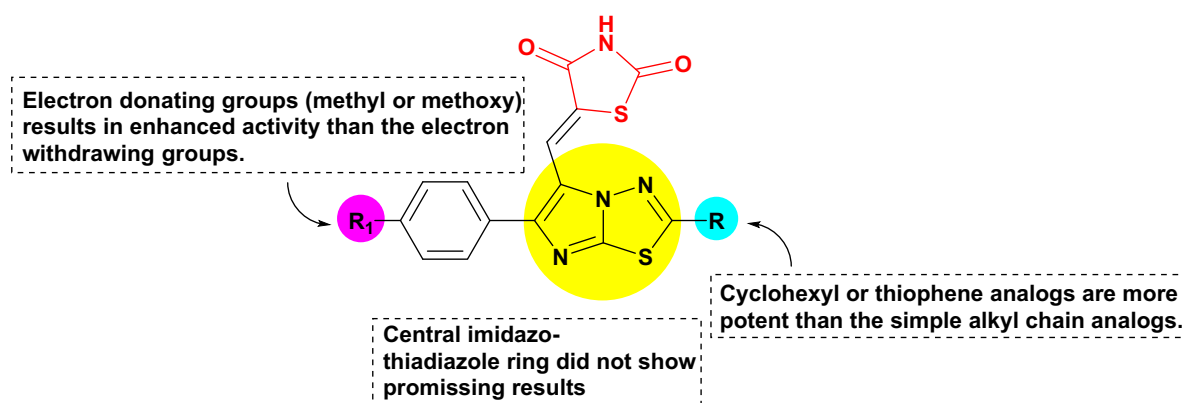


Fig. 9A. SAR of imidazo-thiadiazole based TZD analogs (structures are original and made by using chem draw ultra 12.0).

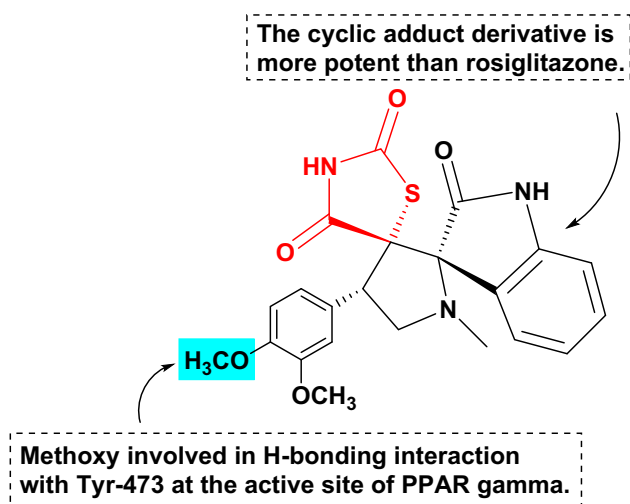


Fig. 9B. SAR of diSpiropyrrolidines based TZD analogs (structures are original and made by using chem draw ultra 12.0).

only three compounds (**219a–c**) showed the most significant and dose-dependent reduction in plasma glucose and TGs level comparable with those in pioglitazone. These three compounds were further evaluated for PPAR- γ agonistic activity using NIH3T3-cells. As a result, compound **219b** showed the maximum PPAR- γ agonistic activity (64%) in comparison to that of pioglitazone (100%) (Table 3 and 4) [107].

SAR of Imidazo-thiadiazole based TZD analogs

Replacement of central benzyl ring with imidazo-thiadiazole ring did not show promising results. Substitution on this ring with cyclohexyl or thiophene analogs may result in better antihyperglycemic activity. Further, substitution with the *p*-methoxyphenyl group on 6th position resulted in good activity [107] (Fig. 9A).

DiSpiropyrrolidines based TZDs

Murugan et al. reported a series of new diSpiropyrrolidines by carrying out 1,3-dipolar cycloaddition reaction as shown in **S40**. Firstly, azomethine ylides (**222**) were obtained by the reaction of isatin (**220**) with sarcosine (**221**), which were further reacted with the double bond of 5-arylidene-TZD derivatives to give the corresponding cycloadducts (**223a** and **b**). The synthesized derivatives were evaluated for antidiabetic activity in alloxan-induced diabetic male Wistar rats by administering the compounds at a dose of 36 mg/kg. As a result, compounds (**223a** and **b**) had shown a better reduction in blood glucose (115.3 and 115.8 mg/dL) levels as compared to rosiglitazone (131.0 mg/dL). Further, compound **223b** also showed the best score (71.18) among all the molecules when docked against PPAR- γ (PDB ID: 1FM9). Also, the compounds were tested for some change in biochemical parameters [serum glutamic pyruvic transaminase (GPT), creatinine, blood urea, liver GPT, and ALP] in the same diabetic model for 15 days. The results showed that levels of these biochemical parameters reduced by the administration of these compounds (Table 4) [108].

SAR of diSpiropyrrolidines based TZD analogs

The cyclic adduct derivatives resulted in more potent derivatives than rosiglitazone. Electron releasing groups at the tail position resulted in interactions with the active site [108] (Fig. 9B).

Acid-based TZDs

Neogi et al. synthesized a series of 2,4-TZD derivatives of phenyl substituted cinnamic acid as shown in **S41**. The first step was to synthesize α -phenyl substituted cinnamic acid (**226**) via Perkin condensation of 3,5-dimethoxybenzaldehyde (**224**) with 4-hydroxyphenylacetic acid (**225**) followed by esterification to give an intermediate (**227**) which upon further condensation with 4-fluorobenzaldehyde furnished compound **228**. Knoevenagel condensation of **228** with TZD gave an intermediate **229** followed by hydrogenation with Pt over carbon afforded the final product, (*Z*)-methyl 3-(3,5-dimethoxyphenyl)-2-(4-(4-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)phenyl)acrylate (**232**). The compound **232** has also been synthesized by reducing aldehyde (**228**) to alcohol (**230**) followed by treatment with PBr₃ yielded bromo compound (**231**) which upon Knoevenagel condensation with TZD (**3**) gave the final compound (**232**). In the final step, the free acid analog of the final compound (**233**) has been synthesized by alkaline hydrolysis of **232**. The synthesized compounds were then evaluated for PPAR- γ agonist activity using HEK-293 cells at different concentrations (0.1 – 30 μ M). It was found that compound **232** came out to be the most potent (EC_{50} = 0.28 μ M) amongst all as compared to rosiglitazone (EC_{50} = 0.009 μ M) whereas compound **233** showed less activity than **232** (EC_{50} = 0.69 μ M). Further, compound **232** was evaluated for its antihyperglycemic activity in *ob/ob* mice for 9 days at a dose of 10 mg/kg in comparison to pioglitazone (20 mg/kg), rosiglitazone (10 mg/kg) and troglitazone (100 mg/kg). As a result, compound **232**, pioglitazone, rosiglitazone, and troglitazone exhibited 29, 25, 42 and 26% reduction in blood glucose levels, respectively. Furthermore, a dose-dependent study was carried out on compound **232** in the same diabetic model at doses of 3.1, 6.3 and 12.5 mg/kg in comparison to troglitazone (12.5 mg/kg) for 19 days. The results showed that the most effective blood glucose-lowering (55%) activity occurred at a dose of 6.3 mg/kg whereas troglitazone caused only a 23% reduction in blood glucose level. In addition, compounds **232** and **233** were evaluated at a dose of 5 mg/kg for 11 days in the same diabetic model. As a result, a similar reduction in blood glucose levels was observed for both the compounds in comparison to vehicle-treated diabetic control mice. These results suggest that the presence of geometry in the cinnamic acid derivative is important for PPAR- γ agonistic activity and thus cinnamic acid-based TZDs can be considered as a lead molecule to discover new antidiabetic agents (Table 3 and 4) [109].

Nazreen et al. synthesized a series of phenoxy acetic acid-based TZDs as shown in **S42**. Initially, different hydroxybenzaldehydes (**234**) were treated with chloroacetic acid (**2**) to furnish different substituted formyl phenoxy acetic acids (**235**) which upon Knoevenagel condensation with TZD (**3**) gives an intermediate (**236**) followed by reduction with sodium borohydride gives the target compounds i.e. 2-(4-((2,4-dioxothiazolidin-5-yl)methyl)-2-methoxyphenoxy)acetic acid (**237a**), 2-(4-bromo-2-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)acetic acid (**237b**) and 2-(4-bromo-2-((2,4-dioxothiazolidin-5-yl)methyl)-6-methoxyphenoxy)acetic acid (**237c**). Firstly, molecular docking studies were carried out against PPAR- γ (PDB ID: 3CS8) and the compounds with glide scores > -6.50 were selected further for PPAR- γ transactivation (HEK-293 cells) by *in vitro* and *in vivo* antidiabetic activity (STZ-induced diabetic rats; 60 mg/kg). The transactivation of PPAR- γ was confirmed through luciferase activity. As a result, compounds **237a–c** showed significant PPAR- γ transactivation (48.35, 54.21 and 55.41%, respectively) than that in control (7%) but the effect of transactivation was not as much of standard drugs, pioglitazone (65.94%) and rosiglitazone (82.21%). The *in vivo* study was carried out using synthesized compounds at a dose of 36 mg/kg for 15 days and revealed the same results as that of *in vitro*. Compounds (**237a–c**) displayed

significant reduction in blood glucose levels (157.5, 158.8 and 159.2 mg/dL), and the effects were comparable to that of standard drugs pioglitazone (134.2 mg/dL) and rosiglitazone (142.2 mg/dL). Further, compound **237c** was evaluated for body weight gain for 15 days and as a resulting compound **237c** showed a significant change in body weight. Then, compounds (**237a–c**) were evaluated for hepatotoxic effects by administering the compounds at 3-times higher (108 mg/kg) than that used in the antidiabetic activity (36 mg/kg). As a result, compounds **237b** and **c** found to be most potent in terms of lowering the levels of AST, ALT, and ALP and did not cause any toxicity/damage to the liver as compared to pioglitazone. Since the compound **237c** showed more potent activity on PPAR- γ transactivation, it was further evaluated for PPAR- γ gene expression in 3T3-L1 cells and the results showed that compound **237c** significantly increased the PPAR- γ gene expression by 2.0-fold in comparison to that of pioglitazone (1.5 fold) and rosiglitazone (1.0 fold) and also increased the levels of GLUT1 and GLUT4. These results demonstrate that **237b** and **c** can be considered as a potential lead molecule for the development of new antidiabetic agents (Table 3 and 4) [110].

Maji and Samanta synthesized a series of TZD-5-acetic acid peptide hybrids as shown in **S43**. The first step was to synthesize 2-(2,4-dioxothiazolidin-5-yl)acetic acid (238) from the reaction of maleic anhydride (141) with thiourea (1) which was then dissolved in dioxane:water (1:1) and the acid was converted to the acid chloride by stirring with SOCl_2 . Then the resulting solution was treated with different esters [single amino acid esters (239), dipeptide methyl ester (240) and tripeptide methyl ester (241)], which was synthesized in the lab to get their corresponding peptide hybrids (**242–244**). The synthesized hybrids were then evaluated for antidiabetic and cardioprotective activities. Firstly, compounds were evaluated for antidiabetic activity *in vitro* by measuring glucose uptake using yeast cells at different concentrations (10, 20, 40, 80, 100 and 200 $\mu\text{L/mL}$). As a result, compounds **242–244** had shown to increase glucose uptake (39.23, 38.19 and 38.80%, respectively), which was similar to that of pioglitazone (42.87%). In addition, these compounds (30 mg/kg) were evaluated *in vivo* for antidiabetic activity using STZ-NA-induced diabetic rats for 14 days. It was found that compounds **242–244** showed a significant reduction in blood glucose level (142, 144.4 and 156 mg/dL, respectively) similar to that of standard pioglitazone (137.8 mg/dL). Further, these hybrids underwent *in vivo* cardioprotective and ECG studies, which demonstrated that **242** and **243** were more

effective in maintaining the cardiac function thereby preventing diabetic cardiomyopathy (Table 3 and 4) [111].

SAR of acid-based TZD analogs

The lowering of blood glucose levels was more when substitution with *o*-phenoxy acetic acid in comparison to *p*-substitution. The activity was lowered as the number of methoxy or alkyl groups increases. The presence of cinnamic acid double bond as well as the geometry of the molecule plays an important role in PPAR agonism [110,111] (Fig. 10A).

Benzylidene based TZDs

Jiwane et al. carried out the reaction on compound 245 with different dialkyl/diarylamines (246) and formaldehyde in the presence of DMF to yield the final product 3-dialkyl/diaryl amino methyl-5-(*o/p*-substituted benzylidene)-TZDs (**247a** and **b**) (**S44**). All the synthesized compounds were screened for their glucose-lowering ability in dexamethasone (1 mg/kg, for 5 days)-induced diabetic rats. Compounds were administered at a dose of 50 mg/kg and the results were compared against rosiglitazone. It was found that compounds (**247a** and **b**) showed significant reduction in blood glucose level (58 and 65%), whereas rosiglitazone reduced blood glucose level up to 88%, which suggested that substitution with α -amino methyl group at 3rd position of TZD showed variations in activity in comparison to rosiglitazone (88%) (Table 4) [112].

Avupati et al. synthesized some novel 2,4-TZDs as shown in **S45**. Reaction of (Z)-4-((2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl)benzaldehyde (248) was carried out by base-catalyzed condensation with substituted aromatic/heteroatomic ketones to yield the final compound, (Z)-5-(4-((Z)-3-(9H-fluoren-2-yl)-3-oxoprop-1-en-1-yl)benzylidene)-TZD (**249**). The title compounds were then screened for antihyperglycemic activity in STZ-NA-induced diabetic rat model. The compounds were administered at different doses (10, 30 and 50 mg/kg) for 1 day and the results were compared with rosiglitazone (10, 30 and 50 mg/kg). The results showed that compound **249** exhibited dose-dependent reduction in plasma glucose levels (39.83%, 44.62% and 52.81% for 10, 30 and 50 mg/kg, respectively) in comparison to rosiglitazone (38.57%, 14.83% and 12.74%, respectively). Further, molecular docking studies were carried out against PPAR- γ (PDB ID: 3CS8) and the compound **249** showed

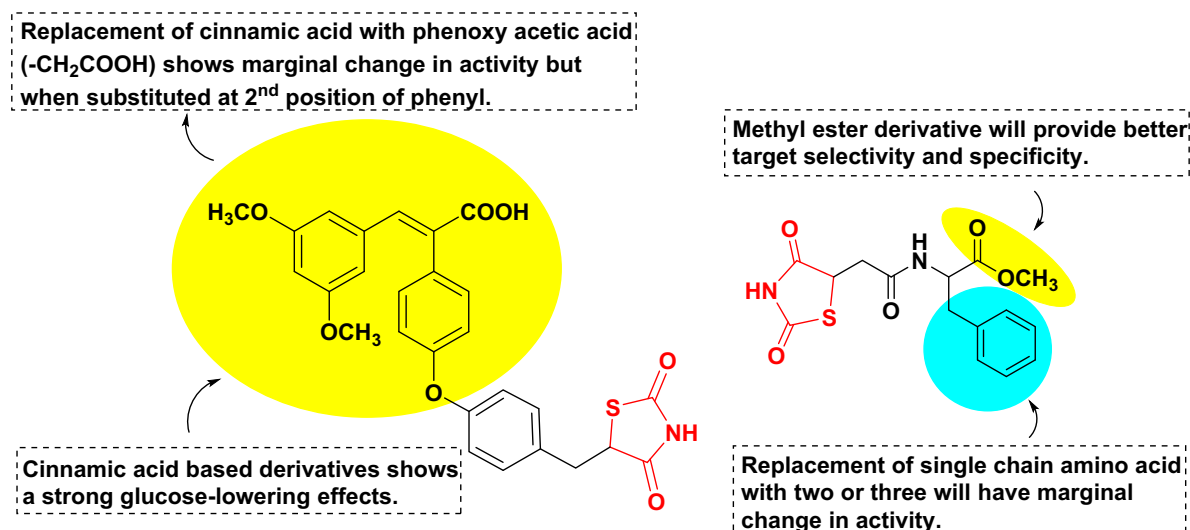


Fig. 10A. SAR of acid-based TZD analogs (structures are original and made by using chem draw ultra 12.0).

–170 dock score as compared to rosiglitazone (–131), which suggested that compound **249** exhibited better binding affinity towards PPAR- γ (Table 4) [113].

Patil et al. synthesized various TZD derivatives as shown in S46. The first step was to synthesize (Z)-5-(4-chlorobenzylidene)-TZD (250) by the Knoevenagel condensation followed by refluxing with metformin (251) in the presence of K_2CO_3 to give the final derivative, (Z)-N¹-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-N²,N²-dimethylhydrazine-1,2-bis(carboximidamide) (**252**). The final derivatives were first evaluated for acute oral toxicity study at a dose of 30 and 100 mg/kg for 2 days and as a result; compounds did not show any signs of toxicity even at 100 mg/kg. So, compounds were further screened for antidiabetic activity in alloxan-induced diabetic rats at 100 mg/kg for 1 day (acute study) and 14 days (subacute study). The effects were observed for the reduction in blood glucose levels in comparison to metformin (100 mg/kg) and pioglitazone (100 mg/kg). The results from the acute study revealed that compound **252** exhibited a significant reduction in blood glucose level (231.4 mg/dL) similar to that of pioglitazone (232.2 mg/dL). The results from the subacute study displayed that compound **252** showed a 65% reduction in blood glucose level to the value close to that of pioglitazone (69%). The most potent compound from the synthesized derivatives was found to be **252**, which showed nearly the same activity as that of the standard compound (pioglitazone) (Table 4) [114].

Patel et al. reported a series of novel 5-[4-(substituted)benzylidene]thiazolidine-2,4-dione along with the evaluation of an antidiabetic activity. Initially, TZD (3) was synthesized by 1, 3 dipolar cycloaddition of thiourea (1) and chloroacetic acid (2) in presence of water (S1). Next, 5-(4-chlorobenzylidene)-2,4-thiazolidinedione (250) was synthesized through Knoevenagel's condensation. The title compounds 5-[4-(substituted)benzylidene]-2,4-thiazolidinediones (**254a-c**) were prepared by microwave-assisted reaction of 5-(4-chlorobenzylidene)-2,4-thiazolidinedione (250) with substituted primary aromatic amines (253) in presence of K_2CO_3 and acetonitrile (S47). The synthesized compounds (30 mg/kg) were evaluated for antidiabetic activity in male Wistar rats through OGTT using pioglitazone (30 mg/kg) as an internal standard. Compounds **254a-c** exhibited potent antidiabetic activity (100–120 mg/dL) similar to pioglitazone (100 mg/dL) (Table 4) [115].

Duhart et al. carried out the in-silico study of 130 TZD derivatives, out of which only two were selected and synthesized in a solvent-free environment as shown in S48. Knoevenagel condensation was carried out between TZD (3) and variously substituted

aldehydes (255) to achieve the desired 5-arylidene-2,4-thiazolidinediones (**256a** and **b**). The synthesized compounds were then tested for acute oral toxicity (14 days) in female Wistar rats by administering the compounds (**256a** and **b**) at a dose of 175, 350, 700, 1400 and 2000 mg/kg in ethanol. As a result, compounds (**256a** and **b**) showed normal behavior and no physical changes were seen but showed fat deposition in the abdominal cavity at a dose ≥ 350 mg/kg. Further, the same compounds were evaluated in the same model at the same doses but in a different vehicle (dimethyl sulfoxide). The results showed that compounds at a dose of 700 mg/kg exhibited severe tiredness along with sedation. One animal at a dose of 1400 mg/kg displayed lethargy for 5 h and hypnosis up to 10 h leading to coma and also showed stomach fundus hardening. Further, the animals receiving 2000 mg/kg were dead within 5 h post-administration on day 1 and showed stomach fundus hardening. So, the doses considered to be safe were 175–1400 mg/kg (Table 4) [116].

Rekha and Chandrashekhara synthesized a series of 5-[4-(substituted)benzylidene]TZDs based on the 2D QSAR studies. Knoevenagel product (257) upon reaction with 1,4-dibromobutane (258) in presence of NaH/DMSO gave another intermediate (259) followed by reaction with various cyclic amines in K_2CO_3 afforded the final compounds, 5-(4-(4-(piperidin-1-yl)butoxy)benzylidene)-TZD (**260a**) and 5-(4-(4-(cyclohexylamino)butoxy)benzylidene)-TZD (**260b**) (S49). The final derivatives were then screened for anti-hyperglycemic effect in dexamethasone (0.7 mg/kg, *i.m.*) induced-diabetic rat model by administering the compounds at a dose of 0.72 mg/kg for 10 days. As a result, compounds (**260a** and **b**) showed a sudden lowering of blood glucose level within 30 min and then showed a constant decrease while the standard drug rosiglitazone showed a decrease in blood glucose level in 30 min (Table 4) [117].

SAR of benzylidene based TZD analogs

The substitution of R with electron-donating groups resulted in a better antidiabetic activity. Substitution of phenyl ring with fluorene moiety resulted in a significant increase in activity in comparison to other aromatic rings (pyridin-2-yl, naphthalene-2-yl). Substitution with bis-guanidine moiety at R position enhanced the activity due to H-bonding with the active site. Substitution on the aromatic ring at the 2nd and/or 4th position with an electron releasing group of the lipophilic site shows good antidiabetic activity than any other position [114–116] (Fig. 10B).

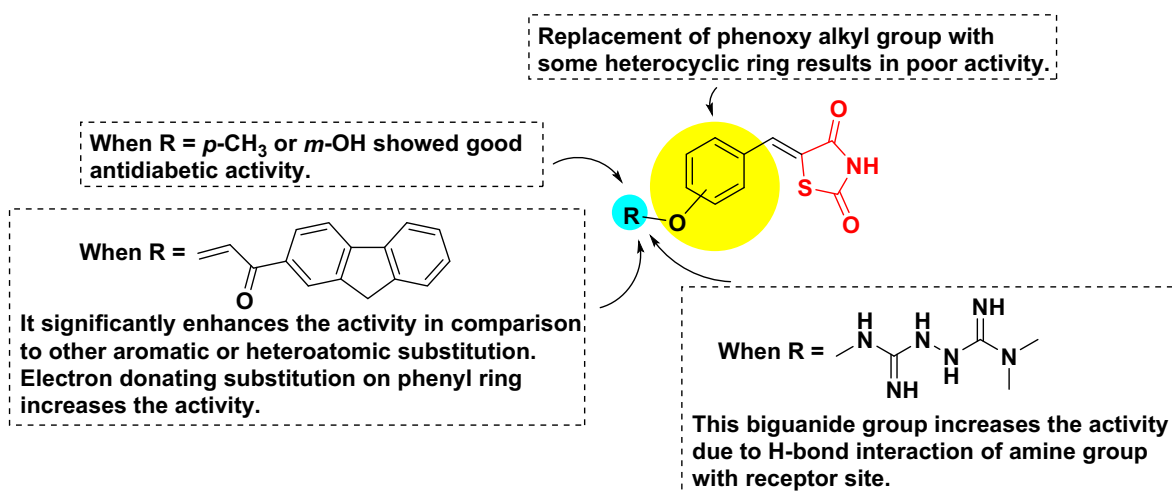


Fig. 10B. SAR of benzylidene based TZD analogs (structures are original and made by using chem draw ultra 12.0).

Benzofused TZDs

Reddy et al. synthesized several TZD derivatives having 5-hydroxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran moieties and their saturated analogs as shown in **S50**. The mesylate (261) was heated with (S)-prolinol to give pyrrolidine derivative (262) which upon reaction with thionyl chloride gave 3-chloropiperidine derivative (263). Compound 263 on reaction with 4-hydroxybenzaldehyde (6) yielded a mixture of 5- and 6-membered ring products (266 and 267). Finally, the mixture of aldehydes (266 and 267) was condensed with TZD to furnish a mixture of unsaturated compounds (**269a** and **270a**) followed by reflux with AcOH-HCl to furnish the debenzylated products (**269b** and **270b**). The saturated TZD analog (268a) was synthesized by treating prolinol derivative (262) with 4-fluoronitrobenzene to give nitro compound (264) followed by reduction gave the amino derivative (265), which upon reaction with TZD gave one of the final compounds (**268a** and **b**). These moieties were then evaluated for their euglycemic and hypolipidemic activity in *db/db* mice. The synthesized derivatives were administered at a dose of 100 mg/kg for 6 days and the reduction in plasma glucose and TG level was compared with troglitazone (200 mg/kg). The results showed that compound **269a** with benzyl protecting group exhibited the most potent plasma glucose (66%) and TG (52%) lowering activities whereas, removing the benzyl protecting group (**269b**) showed poorer plasma glucose (19%) and TG (not active) lowering activities. The related trend was also seen for saturated TZD analogs (**268a** and **b**) but less efficient than compounds **269a** and **b**. As a result, compounds (**268a**, **269a** and **269b**) were further evaluated in the same model at 30 mg/kg for 6 days. It was found that compounds **268a** and **269a** exhibited a good reduction in plasma glucose and TG level but troglitazone was not active at 30 mg/kg. After that, salt forms were prepared for the compounds **268a** (maleate) and **269a** (maleate and HCl) and the results showed that compound **269a** maleate form was the most potent in lowering blood glucose (45%) and TG (42%) level. Further, the dose-dependent study was carried out using **269a** maleate (30 and 100 mg/kg) and troglitazone (30, 100, 200 and 800 mg/kg) for 11 days. The results showed that compound **269a** maleate reduced 70% plasma glucose level at 100 mg/kg whereas troglitazone even at 800 mg/kg showed only 52% plasma glucose reduction. Then, compounds (**268a** and **b**, **269a** and **b**) were evaluated for GAL4-PPAR transactivation by luciferase assay and it was found that none of the compounds was efficient to activate PPAR- α and PPAR- γ as compared to troglitazone. The overall results conveyed that compound, 5-[4-[N-[3(R/S)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2S)-pyrrolidin-2-ylmethyl]phenylene]-TZD (**269a**) was the most potent and efficacious compound as compared to other synthesized derivatives (Table 4) [118].

Jeon and Park prepared TZDs containing benzoxazole moiety with different alkyl substituents. Initially, acetylation of saturated Knoevenagel product (271) was carried out with acetic anhydride to yield an intermediate (272). The compound 272 on *N*-tritylation gave compound 273 followed by deprotection of acetyl group, gave a tritylated derivative (274). Furthermore, 2-chlorobenzoxazole (275) was reacted with substituted alkyl-amino alcohol (91) to give an intermediate (276), which upon Mitsunobu reaction with derivative (274) furnished compound 277 followed by deprotection of trityl group in the presence of TFA gave the final derivative, 5-(3-(2-(benzo[d]oxazol-2-yl(methyl)amino)ethoxy)benzyl)TZDs (**278**) (**S51**). The synthesized derivatives were then screened for PPAR α and PPAR γ transactivation assay using CV-1 cells. As a result, compound **278** showed 113.2% PPAR γ activation while reference standard (GW409544) showed 100% activation (Table 3) [119].

Pattan et al. synthesized a new series of 2-amino[5-(4-sulphonylbenzylidene)-2,4-TZD]-7-chloro-6-fluorobenzothiazole (**283**) as shown in **S52**. Initially, 2-amino-6-fluoro-7-chlorobenzothiazole (280) was synthesized from 3-chloro-4-fluoroaniline (279) in the presence of potassium thiocyanate. Furthermore, condensation of compound 280 and 281 was done in the presence of pyridine and acetic anhydride to synthesize derivative 282. Moreover, compound 282 was reacted with substituted aniline to achieve the final derivatives (**283a-c**). Of note, compound 281 was synthesized by carrying out the chlorosulfonation of benzylidene-TZD. The final derivatives were then evaluated for their antidiabetic activity in alloxan-induced diabetic rats at a dose of 36 mg/kg for one day. It was found that out of all the synthesized derivatives, only three compounds **283a-c** showed the maximum antidiabetic activity in terms of blood glucose-lowering activity (116–123 mg/dL) (Table 4) [120].

Jeon et al. carried out a modified Mitsunobu reaction to synthesize benzothiazole derivatives of TZDs as shown in **S53**. 2-chlorobenzothiazole (284) was reacted with substituted alkylaminoethanols (91) to yield amino alcohols (285). Then, Mitsunobu reaction of 285 was carried out with 5-(4-(4-hydroxybenzyl)TZD (274) in the presence of ADPP and tributylphosphine to yield compound 286 followed by removal of trityl group with the help of TFA furnished the final compound, 5-(4-(2-(benzo[d]thiazol-2-yl(methyl)amino)ethoxy)benzyl)TZD (**287**). The synthesized compounds were evaluated for PPAR transactivation assay and anti-inflammatory activity via NO production using CV-1 cells and RAW 264.7 cells, respectively. As a result, compound **287** which was substituted with methyl on exocyclic nitrogen showed 120% PPAR γ activation as compared to standard i.e., GW409544 (100%) but compound **287** showed lowest anti-inflammatory activity (Table 3) [121].

Purohit and Veerapur carried out the designing, characterization and molecular docking of twelve benzisoxazole containing TZDs. Based on the molecular docking studies carried out against PPAR γ (PDB ID: 2PRG) and Lipinski's rule of five, nine compounds were selected and synthesized as shown in **S54**. 2-((3-phenylbenzo[c]isoxazol-5-yl)(propyl)amino)ethan-1-ol (290) was synthesized by stirring the mixture of 5-chloro-3-phenyl-2,1-benzisoxazole (288), 2-substituted aminoethanol (289) and triethylamine in THF followed by reaction with 5-arylidene TZD in tributylphosphine to get the final product (**291**). The final compounds were then screened for antidiabetic activity in alloxan-induced diabetic-mice at a dose of 30 mg/kg for one day. As a result, compound **291** exhibited the most potent activity in terms of reducing the serum glucose level (-30.62%) than the other synthesized derivatives and the standard drug rosiglitazone (-17.24%) (Table 4) [122].

SAR of benzofused TZD analogs

The substitution of exocyclic nitrogen with methyl enhances PPAR- γ activation. However, on increasing the N-alkyl chain, the activity of TZD analogs decreases; whereas, replacement of benzofuran with benzoxazole or benzisoxazole or benzothiazole selectively activates PPAR- γ [118–122] (Fig. 11A).

Chromones based TZDs

Unlusoy et al. synthesized a series of (Z)-3-methyl-5-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)TZDs (**294**) in order to improve the pharmacological index of insulinotropic activities. The Knoevenagel condensation of 3-formyl chromone (292) with 2,4-TZD (3) yielded 6-methylchromonyl-TZD (293) followed by alkylation with alkyl iodide to furnish the final compound (**294**)

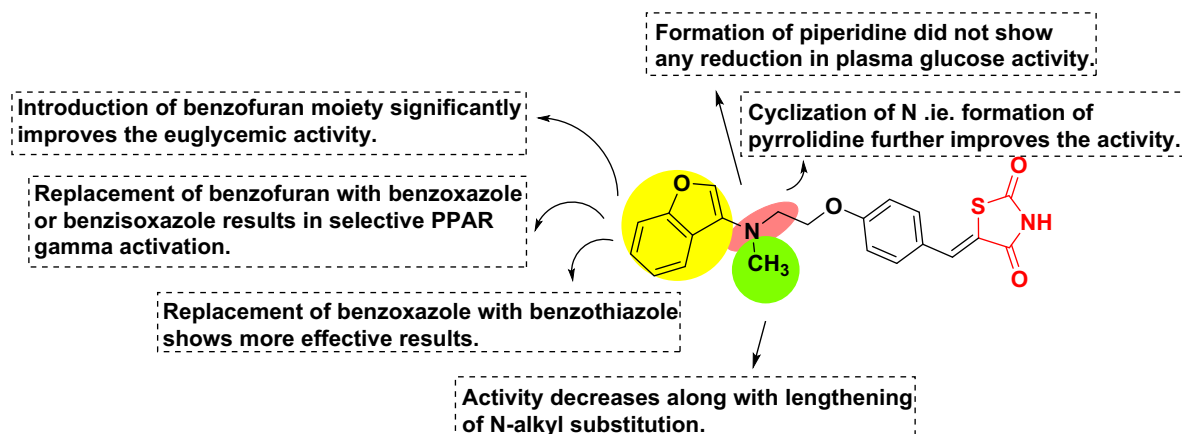


Fig. 11A. SAR of benzofused TZD analogs (structures are original and made by using chem draw ultra 12.0).

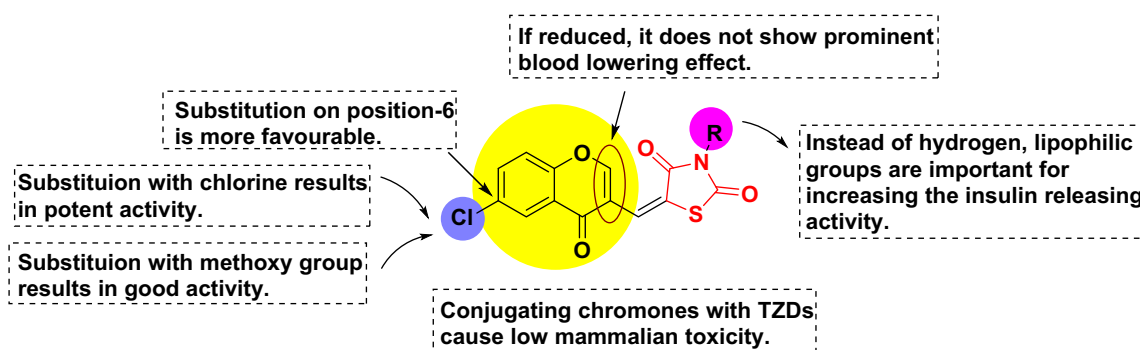


Fig. 11B. SAR of chromones based TZD analogs (structures are original and made by using chem draw ultra 12.0).

(S55). The synthesized compounds were screened for *in vitro* insulin-releasing activity using INS-1 cells at different concentrations (0.001 and 0.01 mg/mL). The results showed that among all the synthesized derivatives, the compound **294** was found to be the most potent at both the concentrations (0.001 mg/mL = 120.6% and 0.01 mg/mL = 152%) in terms of releasing insulin and the results were comparable to glibenclamide (145.7% at 0.001 mg/mL) (Table 3) [123].

Nazreen et al. synthesized a number of chromones based TZD derivatives as shown in S56. The compound **295** was used to synthesize 3-formyl chromones (296), which underwent Knoevenagel condensation with TZD (3) yielded chromonyl-2,4-TZDs (297) followed by catalytic hydrogenation to give the final products, 5-((6-methoxy-4-oxo-4H-chromen-3-yl)methyl)TZD (**298a**) and 5-((6-chloro-4-oxo-4H-chromen-3-yl)methyl)TZD (**298b**) along with by-products (299a and b). The synthesized compounds were first docked against PPAR- γ (PDB ID: 3CS8) and the compounds **298a** and **b** showed -7.57 and -7.76 dock score in comparison to that of rosiglitazone (-5.77). Further, the compounds were evaluated for STZ-induced diabetic rats for 15 days. Compounds **298a** and **b** showed 140% and 135.5% reduction in blood glucose level, respectively as compared to pioglitazone (120%) and rosiglitazone (122%). Compound **298b** was further evaluated for body weight gain for 15 days, as a result, compound **298b** did not show any significant change in body weight, which suggested it showed weight neutral effects. Then, the hepatotoxicity study was carried out with compounds (**298a** and **b**) and as a result, compound **298a** and **b** came out to be most potent in terms of lowering the levels of AST, ALT, and ALP and did not cause any toxic effect to the liver. However, pioglitazone caused mild dilation of sinusoidal spaces. Since, the

majority of drugs used for arrhythmia have been withdrawn due to their ability to cause prolongation of QT interval via blockade of human ether-a-go-go-related gene (hERG), which may lead to syncope and sudden death. Therefore, the compound **298b** was evaluated to ensure whether it has any effect on QT prolongation or not and it was found that it did not cause cardiotoxicity because IC_{50} was found to be 135 μ M. Further, compound **298a** and **b** were evaluated for PPAR- γ gene expression using 3T3-L1 cells and the results showed that compound **298b** significantly increased the PPAR- γ gene expression (45%) in comparison to that of pioglitazone (60%) and rosiglitazone (82%) and also increased the levels of GLUT1 and GLUT4 (Table 3 and 4) [124].

SAR of chromones based TZD analogs

The substitution of the N-3 position of TZD with lipophilic groups resulted in an increased insulin-releasing activity. Reducing the olefinic bonds of chromone ring resulted in a reduced antidiabetic activity. Substitution on chromone ring at sixth position with halogens resulted in more potent compounds as compared to substitution on other positions [123,124] (Fig. 11B).

Miscellaneous targets

Hidalgo-Figueroa et al. carried out the synthesis of TZD derivatives as dual PPAR- α/γ modulator as shown in S57. The compound **300** and **302** underwent Knoevenagel condensation with TZD to produce corresponding derivatives (**301** and **303**). Of note, compounds **300** and **302** were synthesized from 4-bromomethylbiphenyl-2-carbonitrile and ethylbromoacetate with 4-

hydroxybenzaldehyde, respectively. Subsequently, synthesized compounds were evaluated for the relative expression of PPAR- α and PPAR- γ using 3T3-L1 cells. As a result, compound **301** significantly increased the levels of PPAR- γ , PPAR- α and GLUT4. However, compound **303** lacks the activity. Then, compound **301** was docked against PPAR- α and PPAR- γ (PDB ID: 117G and 117I, respectively) and as a result, it gets bind into the active site of both isoforms (α and γ). After that, compound **301** was evaluated for *in vivo* antidiabetic effects in STZ-NA induced diabetic rats at a dose of 50 mg/kg body weight and the results were compared against glibenclamide (5 mg/kg). It was found that compound **301** decreased 32.36% glycemia and the results were comparable with glibenclamide (43.6%) (Table 3 and 4) [125].

Navarrete-Vázquez et al. carried out the synthesis of (Z)-2-(4-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamido)phenoxy)acetic acid (**307**) and evaluated *in vivo* for the relative expression of PPAR- γ , GLUT-4 and PPAR- α . Initially, Knoevenagel condensation of α -chloroacetamide (304) with 4-hydroxybenzaldehyde (6) gave ether-aldehyde (305), which on reaction with TZD (3) yielded compound **306** followed by ethyl ester hydrolysis to give the final derivative (**307**) (S58). Subsequently, compounds (**306** and **307**) were evaluated *in vitro* for PPARs and GLUT4 expression using 3T3-L1 cells. As a result, compounds (**306** and **307**) both increased (2-folds) the relative expression of PPAR- γ and GLUT-4. However, no change was observed in the expression of PPAR- α . Successively, compound **306** (ester pro-drug) was evaluated *in vivo* in STZ-NA induced diabetic rat model at a dose of 50 mg/kg by keeping glibenclamide (5 mg/kg) as a reference drug. It was found that compound **306** decreased 31% glycemia and the results were comparable with glibenclamide (43.6%). Next, the compound **307** was docked against the PPAR- γ (PDB ID: 117I) and as a result, the compound showed important interactions with residues Ser289, His323 and His449 in the active site. The compound **307** has been developed as a potential lead molecule for the treatment of diabetes (Table 3 and 4) [126].

Hidalgo-Figueroa et al. designed two TZD-based derivatives as shown in S59 and evaluated them as antihyperglycemic agents. The final derivatives (**311** and **312**) were synthesized by reacting Knoevenagel product (308) with intermediates (309 and 310, respectively) in basic medium. Subsequently, the compounds were evaluated *in vitro* as PTP1B inhibitors at 20 μ M and as a result, compound **311** decreased the enzyme activity up to 85% whereas compound **312** reduced the activity up to 50%. Therefore, the most active inhibitor was found to be compound **311** on which further concentration–response test has been performed. As a result, compound **311** had shown IC_{50} value of $9.6 \pm 0.5 \mu$ M. In addition, the *in vivo* (STZ-NA induced diabetic rats) activity was performed for compound **311** at a dose of 50 mg/kg body weight and the reference drug was glibenclamide (5 mg/kg). It was found that compound **311** decreased 34% glycemia and the results were comparable with glibenclamide (43.6%). Furthermore, molecular docking studies were carried out against PTP-1B (PDB ID: 1C83) for both compounds **311** and **312**. The compound **311** shown to have the highest affinity with PTP1B in comparison to compound **312**, having a free binding energy of -8.94 Kcal/mol and -8.04 Kcal/mol, respectively (Table 3 and 4) [127].

Conclusion and future perspectives

T2DM is considered as one of the major risk factors for cardiovascular morbidity and mortality. TZDs are reported to increase the transactivation of PPARs thereby, reduce insulin resistance (i.e., reduce gluconeogenesis and increase utilization of glucose and lipid metabolism in the peripheral tissues), which in turn leads to improve the effect of endogenous insulin to maintain the level

of blood glucose. Unfortunately, clinically used TZD class of medications suffered from various serious side effects like hepatotoxicity, edema (fluid retention) and weight gain as a result of troglitazone and rosiglitazone were banned and the pioglitazone has shown to increase the risk of bladder cancer. This review emphasizes TZDs not only as a fortunate and potential scaffold in the field of medicinal chemistry but also outlined the chemistry and biological activities of the TZDs scaffold as antidiabetic agents. The synthetic methodologies signify simplicity and versatility, which offer the medicinal chemist to discover a complete range of novel derivatives. The study also highlighted the SAR studies as well as molecular docking studies in order to carry out future studies on this moiety. Based on this review report, pyrazole, chromone, and acid-based TZD impair the side effects and significantly reduce the blood glucose level than that of clinically used TZDs. Moreover, studies on various approaches such as virtual screening, in-silico drug design, docking etc. can be utilized to develop this class medication for targeting other molecular targets of diabetes to avoid unwanted side effects. Hence, this review will be valuable for the scientific world to develop lead compounds or clinical candidates in various biological areas. Future investigations of pyrazole, chromone, and acid-based TZD scaffold are warranted on other molecular targets of TZD, which can give us more encouraging results. Based on the available study results, TZDs can be considered as one of the promising classes of compounds that can overcome problems of the clinically used TZDs in the management of diabetes.

Compliance with ethics requirement

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The author has declared no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jare.2020.01.008>.

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